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Epimerization of Tertiary Carbon Centers via Reversible Radical Cleavage of Unactivated C(sp^3)-H Bonds

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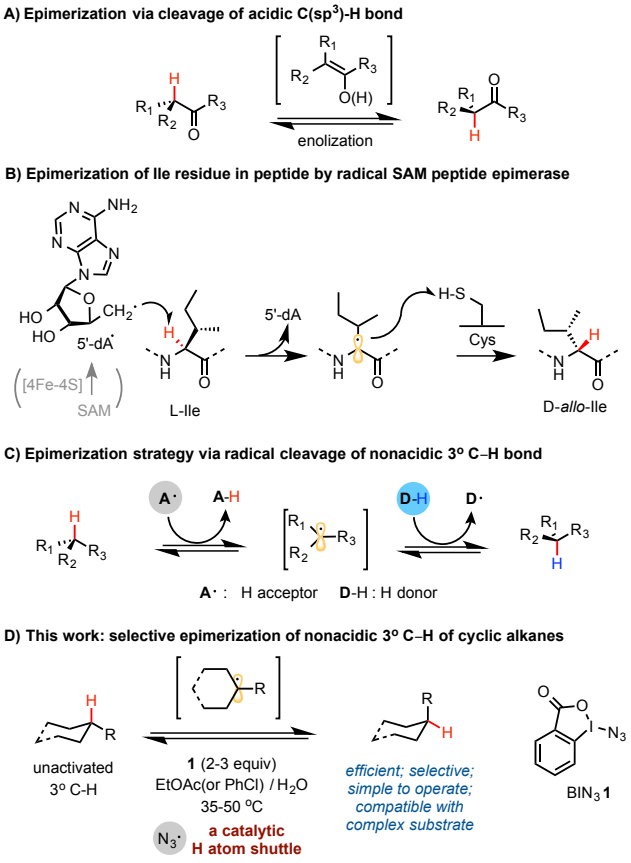
ABSTRACT: Reversible cleavage of C(sp^3)-H bonds can enable racemization or epimerization, offering a valuable tool to edit the stereochemistry of organic compounds. While epimerization reactions operating via cleavage of acidic C(sp^3)-H bonds, such as the Cα-H of carbonyl compounds, have been widely used in organic synthesis and enzyme-catalyzed biosynthesis, epimerization of tertiary carbons bearing a non-acidic C(sp^3)-H bond is much more challenging with few practical methods available. Herein, we report the first synthetically useful protocol for the epimerization of tertiary carbons via reversible radical cleavage of unactivated C(sp^3)-H bonds with hypervalent iodine reagent benziodoxole azide and H_2O under mild conditions. These reactions exhibit excellent reactivity and selectivity for unactivated 3° C-H bonds of various cycloalkanes and offer a powerful strategy for editing the stereochemical configurations of carbon scaffolds intractable to conventional methods. Mechanistic study suggests that the unique ability of N_3• to serve as a catalytic H atom shuttle is critical to reversibly break and reform 3° C-H bond with high efficiency and selectivity.

INTRODUCTION

Methods for the selective functionalization of alkyl C-H bonds have been greatly advanced over the past few decades, offering streamlined strategies for the synthesis and modification of complex molecules.[1-4] A wide range of reactions have been developed to transform C(sp^3)-H bonds into different functional groups.[5-9] However, reactions featuring reversible cleavage of unactivated C(sp^3)-H bonds have received much less attention. Racemization or epimerization via reversible cleavage of C(sp^3)-H bonds might offer an invaluable tool for editing the stereochemistry of organic compounds. Additionally, exchanging C(sp^3)-H bonds with C-deuterium bonds may provide valuable deuterated compounds for biomedical applications.[10,11] Epimerization reactions of tertiary Cα of carbonyl compounds via cleavage of their acidic C(sp^3)-H bonds have been routinely used in the synthesis of complex molecules, and in catalytic process such as dynamic kinetic resolution (**Scheme 1A**). Similar enolization mechanisms have also been widely used by enzyme epimerases for the biosynthesis of natural products.[12] Compared with acidic C(sp^3)-H bonds, epimerization of tertiary carbons bearing non-acidic C(sp^3)-H bonds is much more challenging. Interestingly, recent biochemical studies have shown that [4Fe-4S]-cluster radical S-adenosyl-L-methionine (SAM) epimerases invert the stereocenters of amino acid or sugar units through radical-mediated pathways.[13, 14] For example, an epimerase selectively converts an L-Ile amino acid residue of a peptide to D-*allo*-Ile via abstraction of Cα-H by a 5'-deoxyadenosyl radical (5'-dA•) and quenching of the carbon radical intermediate by a thiol group of an enzyme cysteine residue (**Scheme 1B**).[13] Radical-mediated C(sp^3)-H cleavage reactions could potentially provide a unique solution to epimerize traditionally "unepimerizable" tertiary carbon centers in organic synthesis.



Scheme 1. Epimerization of tertiary carbon via reversible cleavage of tertiary C-H bonds.

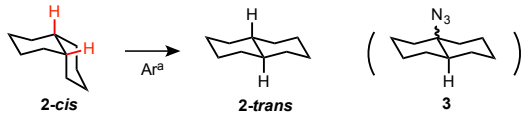
To achieve such transformations with useful efficiency, the sequence of H abstraction by a suitable radical H atom acceptor (A•) and quenching of the tertiary C-radical by suitable H atom donor (D-H) must be developed (**Scheme 1C**). Herein, we report an efficient and synthetically useful protocol for epimerizing tertiary carbons via radical cleavage of non-acidic 3° C(sp^3)-H bonds with hypervalent iodine reagent benziodoxole azide and H_2O under mild conditions (**Scheme 1D**).

RESULTS AND DISCUSSION

Epimerization of *cis*-decalin

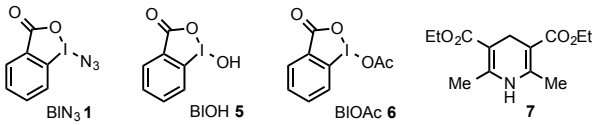
Radical reactions can provide simple and efficient means to selectively cleave 3° and activated 2° C-H bonds of organic compounds due to their relatively weak bond dissociation energy (BDE).[15-20] In the absence of activated 2° C-H bonds, 3° C-H bonds could potentially serve as a unique set of targets for selective radical C(sp^3)-H functionalization of complex substrates. While conventional radical C-H cleavage reactions often require relatively harsh conditions, recent studies have shown radical reactions can take place under much milder conditions.[21-23] Compared with the large number of studies on various radical-mediated functionalizations of 3° C-H bonds, epimerization reactions of tertiary carbons via reversible cleavage of unactivated 3° C-H bonds have been sporadically studied, mostly more than thirty years ago.[24-29] While pioneering works by Mazur,[24,25] Kochi,[26] Hill,[27] and others have demonstrated the feasibility of such a transformation, their methods demand relatively harsh operating conditions such as strong UV irradiation, high temperature or use of toxic reagents (e.g. $HgBr_2$), and exhibit narrow substrate scope.

In 1996, Zhdankin reported that the reaction of simple alkanes with azidobenziodoxole (BIN_3, **1**) in the presence of radical initiator benzoyl peroxide (BzOOBz) at elevated temperature led to selective azidation of 3° C–H bonds (see reaction of model substrate *cis*-decalin **2-*cis*** in entry 1 of **Table 1**).[30] Recently, Hartwig discovered that Fe/PyBOX catalysts promote similar C(sp^3)–H azidation of more complex substrates at room temperature (entry 2).[31] Subsequently, we developed a visible light (VL)-promoted method to affect selective 3° C–H azidation with photosensitizer $Ru(bpy)_3Cl_2$ in hexafluoroisopropanol (HFIP) solvent (entry 3).[32,33] Our visible light-promoted azidation reaction likely starts with the formation of N_3• or benziodoxole (BI•) radicals via single electron transfer (SET) activation of BIN_3.[34-38] These radicals abstract a H atom from 3° C-H bond to form a tertiary C-radical, which then reacts with BIN_3 to give the azidation product. In this VL-promoted system, we noted that C-H halogenation products were obtained in high yield and selectivity when in the presence of halide salts, such as LiCl.[32] This successful modulation of the hypervalent-iodine mediated radical reaction pathway prompted us to attempt C-H epimerization using a combination of H donor (D-H)[39] and BIN_3. As shown in entry 4, we were pleased to see that the desired epimerization product *trans*-decalin **2-*trans*** was obtained in 35% yield when 1 equiv of H-donor Bu_3SnH was included in the reaction mixture. Interestingly, a small amount of **2-*trans*** was formed in the absence of photosensitizer and VL irradiation (entry 5). The yield of **2-*trans*** was improved to 75% when EtOAc solvent was used (entry 6). Use of excess of Bu_3SnH (2 equiv) gave lower yield (entry 7). Use of other H-donors such as $Ph_2P(=O)H$, Et_3SiH, and Hantzsch ester **7** also gave **2-*trans*** in moderate to excellent yield along with small amount of azidation byproduct **3** (entries 8-10). As seen in entry 11, only trace amount of **2-*trans*** was formed in dry EtOAc solvent in the absence of H-donors.



2-*cis* **2-*trans*** **3**

entry	Reagents (equiv), reaction time, temp	Solvents	**2-*trans*** (**2-*cis***) %	**3** %
1	**1** (2), BzOOBz (0.1), 24 h, 80 °C	DCE	<1 (36)	62
2	**1** (2), $Fe(OAc)_2$ (0.1), PyBOX (0.1), 24 h, 23 °C	CH_3CN	<1 (8)	90
3	**1** (2), $Ru(bpy)_3Cl_2$ (0.1%), VL, 24 h, 35 °C	HFIP	<1 (3)	95
4	**1** (2), $Ru(bpy)_3Cl_2$ (0.1%), Bu_3SnH (1), VL, 24 h, 35 °C	HFIP	35 (13)	52
5	**1** (2), Bu_3SnH (1), 24 h, 35 °C	HFIP	7 (34)	59
6	**1** (2), Bu_3SnH (1), 24 h, 35 °C	EtOAc (E)	75 (7)	17
7	**1** (2), Bu_3SnH (2), 24 h, 35 °C	E	10 (89)	<1
8	**1** (2), $Ph_2P(=O)H$ (1), 24 h, 35 °C	E	89 (2)	9
9	**1** (2), Et_3SiH (1), 24 h, 35 °C	E	80 (19)	<1
10	**1** (2), **7** (1), 24 h, 35 °C	E	91 (2)	7
11	**1** (2), 24 h, 35 °C	E (dry)	1 (92)	7
12	**1** (2), 24 h, 35 °C	E (+ 1% H_2O (H))[c]	84 (7)	8
13	**1** (2), 24 h, 35 °C	E/H (9:1)	97 (<1)	<1
14	**1** (2), 24 h, 35 °C	DCE/H (9:1)	87 (2)	10
15	**1** (2), 24 h, 35 °C	PhCl/H (9:1)	95 (2)	3
16	**1** (1), 24 h, 35 °C	E/H (9:1)	90 (9)	<1
17	**1** (0.5), 7 d, 35 °C	E/H (9:1)	95 (4)	<1
18	**1** (0.1), 7 d, 50 °C	E/H (9:1)	69 (30)	<1
19	**1** (0.1), HOAc (0.2), 7 d, 50 °C	E/H (9:1)	80 (19)	<1
20	**5** (2), 24 h, 35 °C	E/H (9:1)	0 (100)	0
21	**6** (2), 24 h, 35 °C	E/H (9:1)	0 (100)	0
22	**1** (2), 24 h, air, 35 °C	E/H (9:1)	0 (95)	(4[d])
23	**1** (2), 24 h, in darkness, 35 °C	E/H (9:1)	97 (1)	1



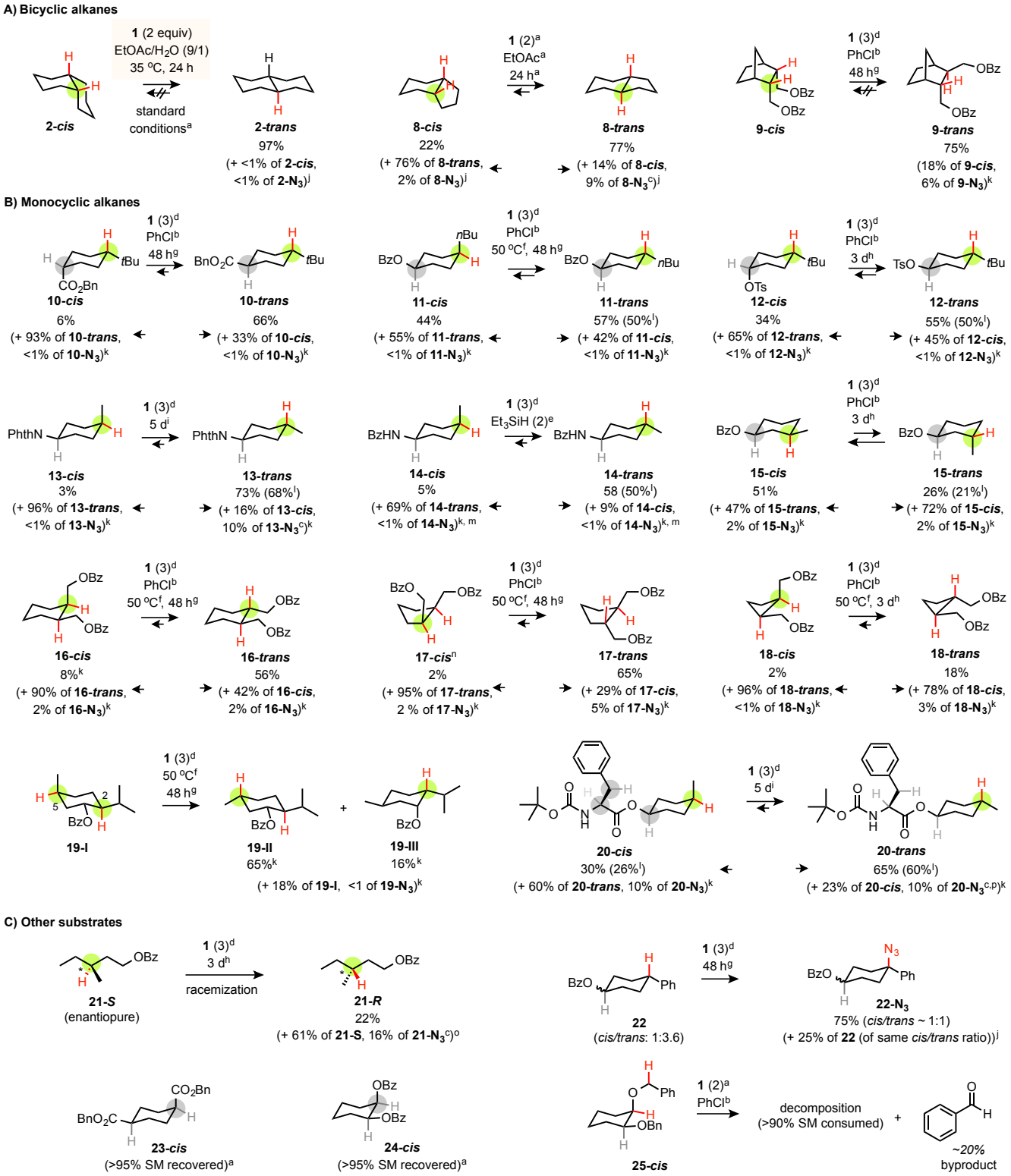
BIN_3 **1** BIOH **5** BIOAc **6** **7**

Table 1. Epimerization of cis-decalin with BIN_3. a) Yields are based on GC-MS analysis of reaction mixture on a 0.1 mmol scale at a 0.2 M concentration using ACS grade solvents under Ar atmosphere unless specified otherwise. Source of VL: 18 W compact fluorescent lamp. b) 2 M concentration. c) EtOAc solvent with 1% of H_2O (~3 equiv) was used. d) 3° C-H hydroxylation side product **4** was obtained in 4% yield. E: EtOAc, H: H_2O.

Surprisingly, a clean epimerization with almost complete suppression of azidation was observed when a mixture of EtOAc/H_2O (9:1) was used (entry 13). A mixture of PhCl/H_2O gave comparable results. (entry 15). The use of 0.1 equiv of BIN_3 over an extended reaction time (7 days) at 50 °C led to 69% yield of **2-*trans***, suggesting a catalytic pathway in the BIN_3-mediated epimerization reaction (entry 18). In contrast to BIN_3, other benziodoxole reagents such as hydroxybenziodoxole BIOH **5** and acetoxybenziodoxole BIOAc **6** exhibit no reactivity (entries 20, 21). A trial conducted under an air atmosphere gave only trace amount of C-H hydroxylation side product **4** (entry 22). Irradiation with visible light had no impact on the epimerization reaction (entry 23).

Substrate scope and selectivity

With the optimized conditions in hand, we next explored the scope of this BIN_3/H_2O-mediated C-H epimerization reaction with representative mono-, bicyclic and acyclic alkanes bearing suitable 3° C(sp^3)-H bonds (**Scheme 2**). In general, the efficiency of the



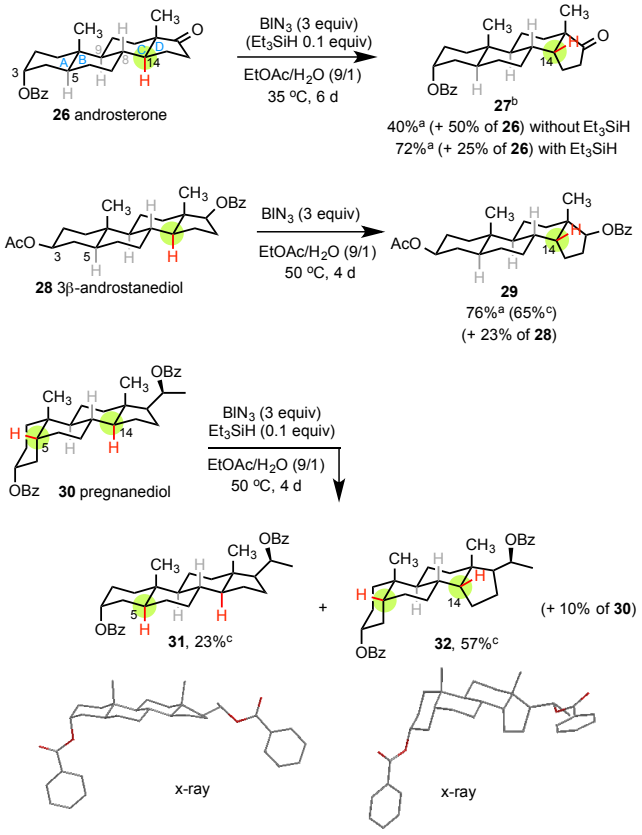
Scheme 2. Substrate scope of BIN_3/H_2O-mediated 3° C-H epimerization. a) Standard reaction conditions: 0.1 mmol of alkane, 0.2 mmol of BIN_3, EtOAc/H_2O (0.45/0.05 mL), 35 °C, Ar, 24 hours unless specified otherwise. b) EtOAc is replaced with PhCl. c) More azidation byproduct is formed in PhCl/H_2O than in EtOAc/H_2O. d) BIN_3 (3 equiv). e) Additional Et_3SiH (2 equiv). Significant oxidation at NH-adjacent 3° C-H occurred in the absence of Et_3SiH. f) Reaction temperature: 50 °C. g) t = 48 h. h) t = 3 d. i) t = 5 d, j) Yields are based on GC-MS analysis. k) Yields are based on ^{1}H-NMR analysis. l) Isolated yield. m) about 20% of benzamide byproduct was formed. n) A *cis*/*trans* (3/1) mixture was used. o) Yields are analyzed by chiral HPLC. p) azidation of 3° C-H bond. SM: starting material.

epimerization reactions correlates well with the relative thermodynamic stability of the corresponding epimers. Reactions of epimers with small free energy difference are bidirectional and give similar product distribution from either epimer starting material, indicating

the ability to reach epimerization equilibrium (see **8**, **11**). Reactions of epimers with large free energy difference are unidirectional, predominantly giving the more stable epimer (see **2**, **9**). The site and chemo-selectivity of this C-H epimerization is strongly influenced by the BDE of C-H bonds and electronic effects. Electron-rich 3° C-H bonds of cyclic alkanes are most reactive, forming only small amount of azidation byproducts (typically less than 5%). Electron-withdrawing groups such as alkoxylcarbonyl (e.g. CO_2Bn) and carboxylate oxygen (e.g. BzO) not only diminish the epimerization reactivity of neighboring 3° C-H bonds but also lead to more C-H azidation byproduct. Compared to electronic effects, steric effects appear to have a less significant impact on the reactivity (see **10**, **12**).

As shown in **Scheme 2A** and **2B**, the epimerization of 5- and 6-membered mono- and bicyclic alkanes generally works well. While the reactions of 1,4 or 1,2-disubstituted cyclohexanes (**10-14**, **16**) favor the formation of more stable *trans* isomers, the reaction of 1,3-disubstituted cyclohexane **15** slightly favors the more stable *cis*-isomer **15-cis**. Functional groups such as benzoate (**9**), benzyl ester (**10**), phthalimide (**13**), BocNH (**20**), and tosyl (**12**) were tolerated. Free OH, SH, NH_2 and CO_2H groups are incompatible with the reaction conditions. Epimerization of isomenthol benzoate **19-I** takes place at either C_5 or C_2 position to give a mixture of **19-II** (65%) and **19-III** (16%). The epimerization of Boc-protected phenylalanine ester **20-*cis*** selectively occurs at the 3° C-H bonds of cyclohexane without reaction at the acidic Hα of the amino acid. In comparison, epimerization reactions of **20-*cis*** under the known UV-irradiation conditions with acetone, $HgBr_2$, or polyoxometalate gave much lower yield.[40] Reaction of **14-cis** bearing a secondary amide group BzNH under standard conditions gave a complex mixture. However, the reaction was improved with the addition of 2 equiv of Et_3SiH. Including Et_3SiH in the reaction mixture improved the epimerization performance in some cases (see **Scheme 3**). The lack of reactivity observed with **23-*cis*** and **24-*cis*** indicates that electron-withdrawing CO_2Bn and BzO groups deactivate their adjacent 3° C-H bond (**Scheme 2C**).[41] Accordingly, the epimerization of **10-15** should occur at the more electron-rich 3° C-H bonds highlighted in green. Reactions in EtOAc/H_2O usually gave less C-H azidation byproduct than in PhCl/H_2O (see **8** and **13**). The epimerization reactivity of electronically deactivated substrates can be slightly improved with PhCl /H_2O solvents (see **9** and **17** bearing two electron-withdrawing OBz groups). Compared with cyclohexane **16** and cyclopentane **17**, the lower epimerization efficiency of **18** may be caused by the higher BDE of the cyclobutane 3° C-H bonds. No epimerization reaction was observed for the corresponding cyclopropane substrate due to its even higher 3° C-H BDE. These OBz-protected substrates were easily prepared in two steps from the corresponding commercially available carboxylic acids.[42] Compared with the clean epimerization reactions of benzyloxycarbonyl, benzoate and tosylate substrates (e.g. **10**, **11**, **12**), a trial with benzyl ether **25-*cis*** gave a complex mixture and benzaldehyde byproduct, presumably caused by oxidation of the benzylic C-H bond. As indicated by the slow racemization of **21-S**, 3° C-H bonds of acyclic alkanes are less reactive than the 3° C-H bonds of cyclic alkanes. In **22**, the target 3° benzylic C-H bond gave mostly azidation byproduct **22-N_3** possibly due to the low H abstraction reactivity of the corresponding benzyl radical intermediate.

As shown in **Scheme 3**, this epimerization protocol has been successfully applied to steroid substrates bearing multiple 3° C-H bonds. Reaction of androsterone benzoate **26** selectively gave the C_{14}-epimer **27** with a cis C/D ring juncture in good yield under slightly modified conditions with the addition of 0.1 equiv of Et_3SiH. Reaction of androstanediol derivative **28** gave C_{14}-epimer **29** in 65% isolated yield. The epimerization of pregnanediol dibenzoate **30** took place at either C_5 or C_{14} position to give a diastereomeric mixture of **31** (23%) and **32** (57%). The structures of epimerization products have been confirmed by X-ray crystallography.

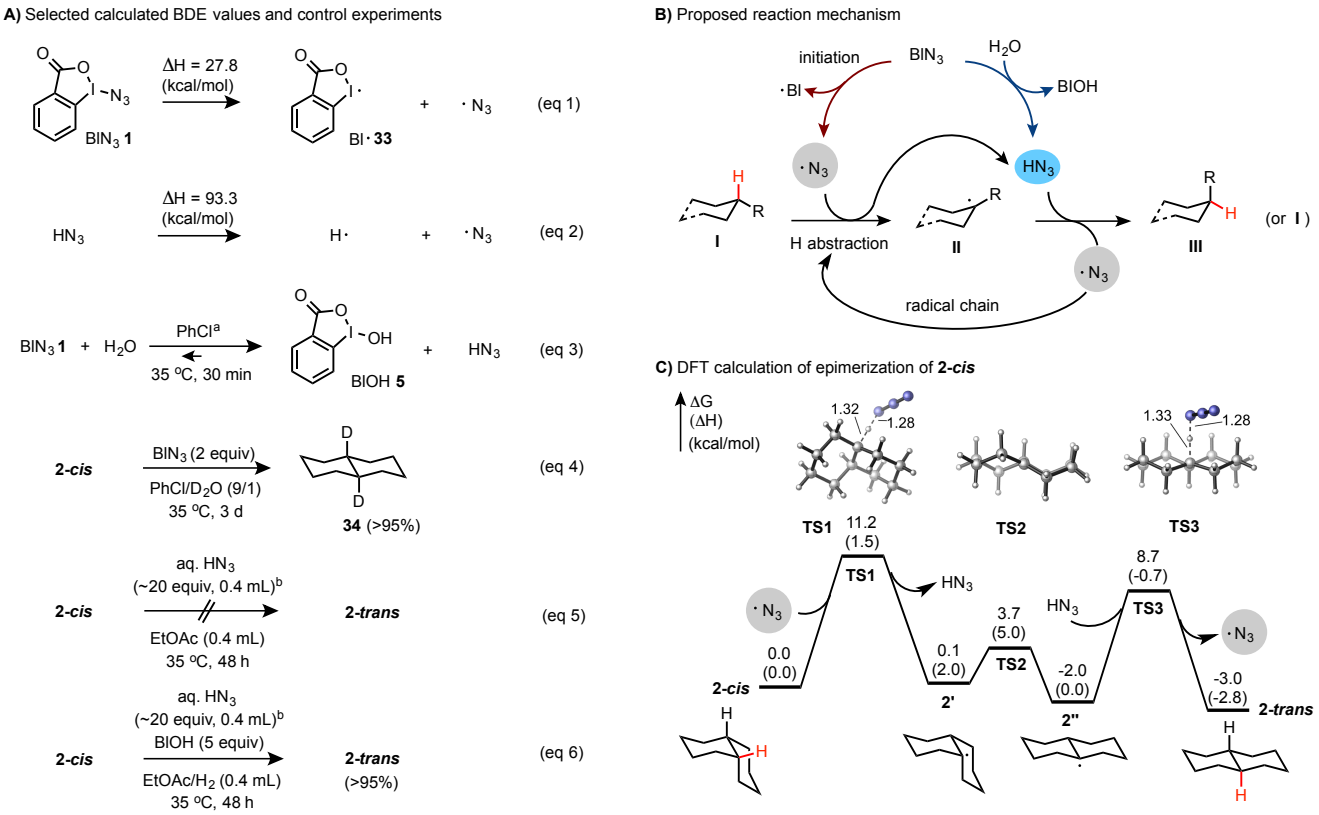


Scheme 3. 3° C-H epimerization of steroids. Reactions are conducted on a 0.1 mmol scale. a) Yields are based on ^{1}H-NMR analysis. b) Structure of its oxime derivative was confirmed by X-ray crystallography. c) Isolated yield. See SI for detailed X-ray structures.

Mechanistic Studies

Control experiments and density functional theory (DFT) calculations have been carried out to understand the mechanism of this BIN_3/H_2O-mediated C(sp^3)-H epimerization reaction. As outlined in **Scheme 1C**, a radical 3° C-H epimerization reaction would require efficient H-abstraction by a H-acceptor (A•) as well as selective quenching of the resulting carbon radical intermediate by a H-donor (D-H). Ideally, A• should not react with D-H, avoiding nonproductive consumption of donor and acceptor.[43-48] Furthermore, competing reaction pathways of the carbon radical intermediates need to be suppressed to achieve clean epimerization. 1) Previous studies have shown that BIN_3 is uniquely effective at initiating the C-H activation step through the formation of H-acceptor Bl• **33** or N_3• via dissociative SET or homolytic cleavage of I-N bond (**Scheme 4A**).[32] In this reaction system, homolytic I-N cleavage of BIN_3 is expected to occur at ambient temperature in the absence of light irradiation. This is supported by the DFT calculations that indicated a very small BDE of 27.8 kcal/mol for the Bl-N_3 bond (eq 1), compared to the calculated I-O BDEs for Bl-OH **5** and Bl-OAc **6** (42.3 and 42.5 kcal/mol, respectively). More importantly, H-N_3 has a

Scheme 4. Mechanistic studies.



DFT calculations were performed at the M06-2X/6-311++G(d,p)-SDD/SMD(EtOAc)//M06-2X/6-31+G(d)-SDD/SMD(EtOAc) level of theory, See Supporting Information for more details. a) 64% yield of **5** was formed for forward reaction of **1** (1 equiv) in PhCl/H_2O (9/1, H_2O ~ 9 equiv). 5% yield of **1** was formed for reverse reaction of **5** (1 equiv) and aq. HN_3 (~ 3 equiv) in PhCl/H_2O. b) aq. solution of HN_3 [~5 M] is prepared from reacting NaN_3 with aq. H_2SO_4 at rt (see Supporting Information).

BDE of 93.3 kcal/mol, which is very close to the BDE of unactivated 3° C-H bonds (93.3 and 96.1 kcal/mol for 3° C-H of ***2-cis*** and ***2-trans***, respectively, **Scheme 4C**). In comparison, the 2° C-H bonds of cyclohexane have a larger BDE of 97.5 kcal/mol. The close match in BDE of H-N_3 and unactivated 3° C-H not only renders N_3• a competent H-acceptor for 3° C-H bonds but also makes H-N_3 a suitable H-donor to 3° carbon radical intermediates, making N_3• an effective hydrogen atom shuttle for 3° C-H bonds. 2) Although H_2O is critical to the success of this epimerization reaction, H_2O is unlikely the immediate H-donor due to the high BDE of H-OH (~ 117.2 kcal/mol).[49] Control experiments indicate that BIN_3 readily reacts with H_2O to form BlOH **5** and HN_3 in EtOAc or PhCl (>60% conversion in 30 min, eq 3). Furthermore, reacting BlOH with aq. HN_3, prepared by mixing NaN_3 with aqueous H_2SO_4, can also form small amount of BIN_3, suggesting a reversible reaction of BIN_3 and H_2O. Reaction of ***2-cis*** using D_2O as co-solvent gave the deuterated product **34** in excellent yield (eq 4), suggesting DN_3 as the deuterium donor. 3) As shown in eq 5, the use of aq. HN_3 alone did not give any epimerization product under the reaction conditions. Similarly, BlOH alone cannot promote the epimerization reaction (entry 20, Table 1). However, a combination of BlOH and aq. HN_3 is effective (eq 6). These results suggest that the residual BIN_3, rather than HN_3 or BlOH, is responsible for the initiation of C-H epimerization.[32] Since BIN_3 is an excellent azidation reagent for carbon radicals, the low concentration of BIN_3 and the abundance of HN_3 in the reaction system might contribute to the suppression of the competing C-H azidation pathway. 4) As outlined in the proposed reaction pathway in **Scheme 4B**, this epimerization reaction likely starts with a homolytic cleavage of the residual BIN_3, generating Bl• **33** and N_3• radical. N_3• then selectively cleaves a 3° C-H bond of alkane **I** forming carbon radical **II** and HN_3.[38] In additional to the steric hindrance and C-H bond nucleophilicity, the 1,3-diaxial strain release and torsional strain factor concerning the tertiary radical transition state would also influence the reactivity of H abstraction.[50-52] Nucleophilic carbon radical **II** then reacts with the electrophilic H-donor HN_3[53] to give the epimerization product **III** or **I** and regenerate N_3•, thus propagating a radical chain reaction. As shown in **Scheme 4C**, DFT calculations of the epimerization of *cis*-decalin ***2-cis*** show that both the initial H abstraction by N_3• (**TS1**) and the subsequent quenching of tertiary carbon radical with HN_3 (**TS3**) proceed with low energy barriers.[54-57] The late transition state (r(C-H) = 1.32 Å in **TS1**) suggests the rate and selectivity of the C-H abstraction are sensitive to the BDE of the C-H bonds.[57] DFT calculations also indicate the more sterically hindered Bl• **33** is less effective than N_3• at cleaving the 3° C-H bond of ***2-cis*** (see Supporting Information for details). Overall, the facile activation of BIN_3 at ambient temperature, the proper equilibrium between BIN_3 and HN_3 in the presence of H_2O, and the unique ability of N_3• as a catalytic hydrogen atom shuttle enable an efficient, selective and clean radical 3° C-H epimerization under mild conditions.

Conclusion

In summary, we have developed the first synthetically useful protocol for radical-mediated C-H epimerization reactions of tertiary carbon centers, using a hypervalent iodine reagent and H_2O under mild conditions. These reactions show excellent reactivity and selectivity toward unactivated 3° C-H bonds of various cycloalkanes and offer a powerful tool to edit stereochemical configurations that are intractable by conventional methods. Using this method, we have demonstrated easy access to novel steroid scaffolds. We hope that use of N_3• as a catalytic hydrogen atom shuttle for unactivated C(sp^3)-H bonds might facilitate other challenging radical C-H functionalization transformations, such as C-H deuteration and dynamic kinetic resolution, in future investigations.

ASSOCIATED CONTENT

Detailed synthetic procedures, compound characterization, NMR spectra, X-ray crystallographic data, and computational details are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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The authors declare no competing financial interest.

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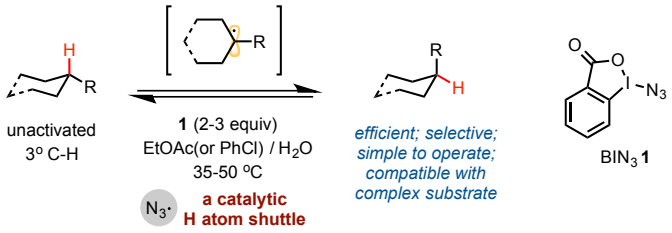
H
R
unactivated
3° C-H
R
1 (2-3 equiv)
EtOAc(or PhCl) / H2O
35-50 °C
N3·
a catalytic
H atom shuttle
R
H
efficient; selective;
simple to operate;
compatible with
complex substrate
O
O
I
N3
BIN3 1