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Recyclable Hypervalent-Iodine-Mediated Dehydrogenative Cyclopropanation under Metal-Free Conditions

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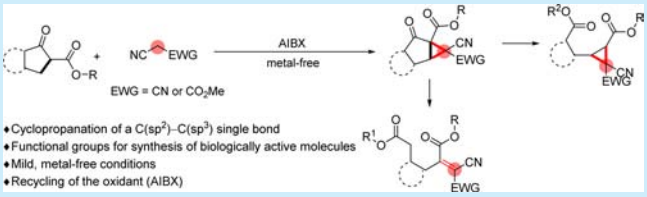
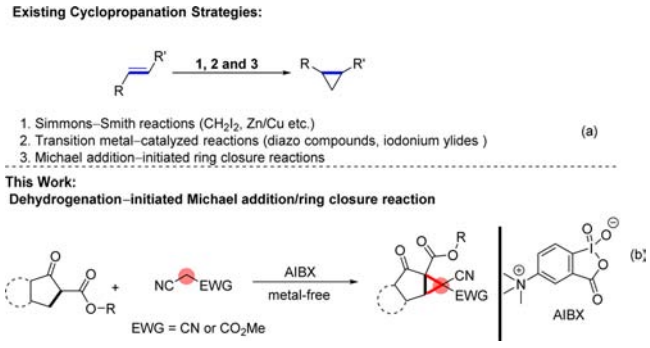
Supporting Information

ABSTRACT: A method is developed for the synthesis of cyclopropanes from the C(sp^2)−C(sp^3) single bonds of β-keto esters with activated methylene compounds under metal-free conditions in the presence of 5-trimethylammonio-1,3-dioxo-1,3-dihydro-1λ^5-benzo[d][1,2]iodoxol-1-ol anion (AIBX), a recyclable water-soluble hypervalent iodine(V) reagent developed by our group. This mild, efficient method has a wide substrate scope and good functional group tolerance and is complementary to existing cyclopropanation strategies. The method can be used to construct polysubstituted ring-fused cyclopropanes and is amenable to further synthetic transformations for construction of complex biologically active molecules as well as asymmetric cyclopropanes (90% de) when a chiral ester auxiliary is used.



Cyclopropane moieties are present in a range of synthetic compounds, bioactive natural products, and drugs.[1] Cyclopropanes are also important synthetic building blocks due to the highly strained ring. Release of ring strain by ring opening, which occurs readily (particularly for donor−acceptor cyclopropanes), provides the driving force for much of cyclopropane chemistry.[2] Numerous approaches to cyclopropane synthesis have been developed (Scheme 1a). Many of the approaches, including Simmons−Smith reactions,[3] transition-metal-catalyzed addition reactions of alkenes with diazo compounds or iodonium ylides,[4] Michael addition-initiated ring-closure (MIRC) reactions,[5] and others,[6] start from alkenes or unsaturated carbonyl compounds. Among them, metal agents are not involved in MIRC reactions and cyclopropanation initiated by hypervalent iodine reagents,[6b−d] hyperiodite,[6a] and several other scattered examples.[6e−h] To our knowledge, cyclopropanation of a C−C single bond, especially under metal-free conditions, has never been achieved. The ring-fused cyclopropane scaffold is a prevalent structural unit in synthetic chemistry owing to its unique chemical reactivity involving fragmentation and rearrangement.[7] This scaffold is typically constructed via intramolecular cyclization reactions between olefins and tethered C1 synthons such as metal carbenoids.[8] Synthesis of its polysubstituted analogues is challenging.

Scheme 1. Approaches to Cyclopropane Synthesis



As part of our ongoing exploration of oxidative reactions brought about by hypervalent iodine reagents,[9] we herein report the oxidative α,β'-cyclopropanation of saturated β-keto esters under metal-free conditions, which constitutes a facile method for the construction of polysubstituted bicyclo[3.1.0] scaffolds via dehydrogenation-initiated Michael addition and subsequent ring closure (Scheme 1b).

We began our exploration by using *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1a**) to react with malononitrile (2.0 equiv) in the presence of 2.5 equiv of 5-trimethylammonio-1,3-dioxo-1,3-dihydro-1λ^5-benzo[d][1,2]-iodoxol-1-ol anion (AIBX) in a solution of 3:1 (v/v) CH_3CN/water at 40 °C, affording cyclopropane **2a** in 65% yield within 12.5 h, and the structure of **2a** was confirmed by X-ray crystallography (Figure 1).[10] Further investigation of reaction conditions for the dehydrogenative cyclopropanation revealed that a system consisting of 2.0 equiv of malononitrile, 2.5 equiv of AIBX, and 1.0 equiv of AcOH in 1:3 (v/v) CH_3CN/water at 40 °C was optimal (for details, see the Supporting Information).[11]

Using the optimal conditions, we carried out reactions of a series of β-ketoesters to explore the generality of the reaction (Scheme 2). Substrates bearing electron-donating substituents

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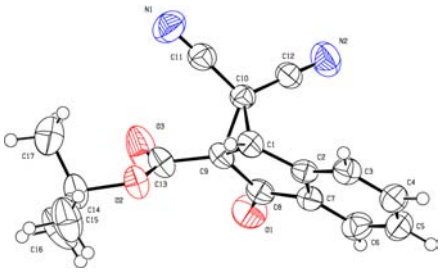
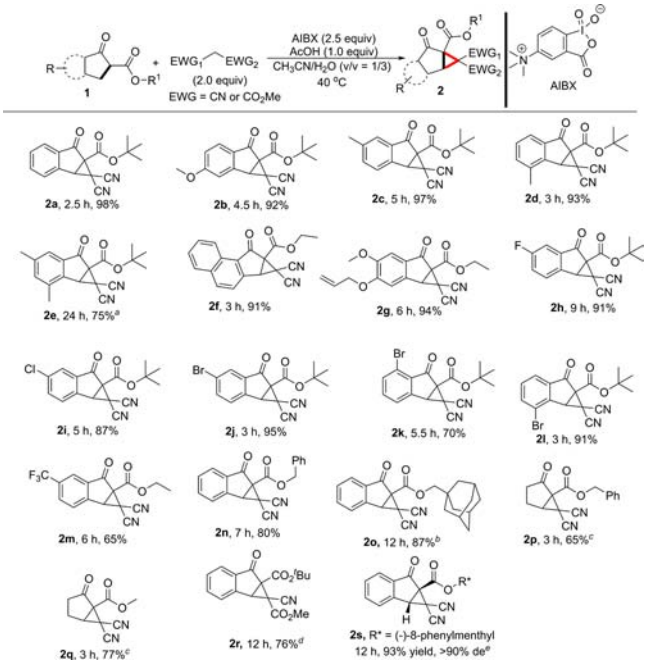


Figure 1. Single-crystal X-ray structure of **2a**.

Scheme 2. Substrate Scope

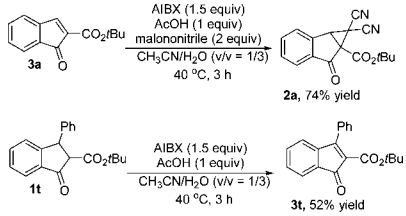


[a]Reaction carried out in 1:1 (v/v) CH_3CN/H_2O. [b]Reaction carried out in 1:1:3 $CH_3CN/THF/H_2O$. [c]Camphorsulfonic acid was used as additive instead of AcOH. [d]Reactions in 2:3 CH_3CN/H_2O. [e]The de value was determined by ^1H NMR spectroscopy.

(Me, OMe) on the phenyl ring were smoothly converted to the desired cyclopropane products in good to high yields (**2b**–**2e**), and it was notable that substrates bearing one or two methyl groups on the phenyl ring yielded the desired products without undergoing benzylic oxidation. A substrate with a readily oxidizable naphthalene ring tolerated the oxidative conditions, giving the desired product (**2f**) in excellent yield. The allyloxy group in substrate **1g** remained intact under the cyclopropanation conditions, affording **2g** in 94% yield. We also obtained excellent yields of halogen-substituted cyclopropanes (**2h**–**2l**), which contain reactive handles for construction of more complex molecules. Substrates bearing benzyl and (adamantan-1yl)methyl ester moieties smoothly afforded the corresponding cyclopropanated products (80% and 87%, respectively). Furthermore, cyclopropanation could be accomplished even with fully saturated substrates: specifically, **2p** and **2q** were obtained in 65% and 77% yields, respectively, in the presence of camphorsulfonic acid as an additive.[12] Methyl α-cyanoacetate was also a suitable nucleophile, affording a single regioisomer (**2r**) under the optimal conditions (for structural information obtained by crystallographic analysis, see the Supporting Information, Section VI).[13] A substrate with an (−)-8-phenylmenthyl group as a chiral auxiliary underwent efficient stereoselective cyclopropanation to furnish a product bearing two contiguous stereogenic centers (**2s**, 93% yield, 90% de).

To investigate the mechanism of this transformation, we carried out several control experiments (Scheme 3). First, cyclic

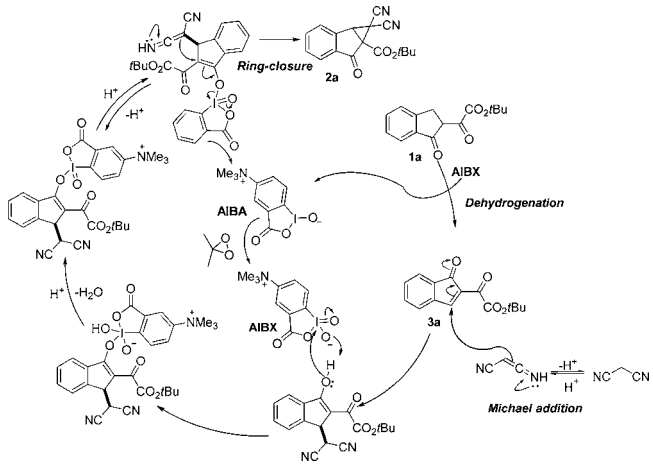
Scheme 3. Control Experiments



enone **3a** was prepared[14] by means of a reported method with PhSeCl/pyridine and subsequent oxidation with hydrogen peroxide. When **3a** was cyclopropanated under the standard conditions, except that 1.5 equiv of AIBX was used, the reaction smoothly gave the desired product (74%, Scheme 3a), confirming the intermediacy of an enone. When substrate **1t**, a **1a** analogue bearing a β'-phenyl group, was allowed to react with 1.5 equiv of AIBX in the absence of malononitrile, enone **3t** was obtained in 52% yield (Scheme 3b), a result that provides direct evidence for the dehydrogenative reactivity involved in the cyclopropanation mechanism.

On the basis of our previous work on AIBX-initiated reactions[9] and the results of the above-described experiments, we propose the mechanism shown in Scheme 4. First, enone **3a**

Scheme 4. Plausible Reaction Mechanism



is produced via AIBX-mediated dehydrogenation, as confirmed by the control experiment shown in Scheme 3a. Under the acidic conditions, Michael addition of malononitrile to **3a** can be expected to occur readily. The nucleophilic hydroxyl group of the resulting adduct attacks the iodine center of another molecule of AIBX to give a reactive iodine(V) complex. Finally, after elimination of a molecule of water, intramolecular oxidative cyclization driven by the release of one AIBA molecule gives **2a**.

Because AIBX is highly water-soluble (0.38 M), it can be regenerated (above 90%) after the reaction by (1) removal of the organic components by extraction with EtOAc, (2)

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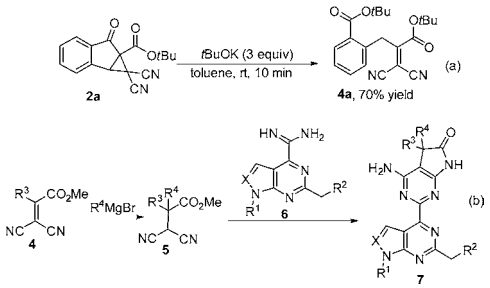
evaporation of the aqueous phase to give reduced form of AIBX, and (3) oxidation of the reduced AIBX with dimethyl dioxirane.

Next we explored the reactivity of the polysubstituted bicyclo[3.1.0] scaffold obtained from the cyclopropanation reaction. When **2a** was treated with *t*BuOK in toluene (Scheme 5a), fission of the C−C bonds in both the cyclopentanone and

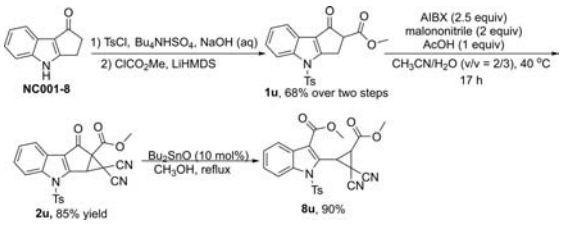
Scheme 5. Ring Opening of the Bicyclo[3.1.0] Scaffold and Synthesis of Compounds 7



the cyclopropane moieties produced tetrasubstituted alkene **4a** (70%), which bears geminal cyano groups at the terminal end of the alkene and an ester at the other end. This type of alkene can serve as a key component in the preparation of polyfunctionalized indolines, quinoxalin-2-ones, pyrazolopyridines, and pyridazines.[15] In addition, it is the key intermediate in the synthesis of compounds **7** (Scheme 5b), which can activate soluble guanylate cyclases and thus are valuable for the prevention and treatment of cardiovascular disease.[16] The smooth formation of **4a** suggests that a series of dicyanoalkene analogues **4** could be produced by treatment of the compounds shown in Scheme 2 with *t*BuOK. We surmise that the synthetic route shown in Scheme 5b could be used to transform dicyanoalkenes **4** into a library of active analogues of **7**.

Indole motifs are common in natural products, pharmaceuticals, and agrochemicals, and more than 200 indole-based compounds are currently marketed as drugs or are undergoing clinical trials.[17] Because of the importance of these motifs, we used our method to derivatize indole-based substrates. Compound **1u** was synthesized from 3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one (NC001-8), a drug candidate for treatment of spinocerebellar ataxia type 3 and other polyglutamine-mediated diseases,[18] after sequential *N*-protection and methoxycarbonylation (Scheme 6). When **1u** was subjected to the

Scheme 6. Indole Derivatization



optimal cyclopropanation conditions (except that a larger amount of acetonitrile was used), **2u**, which has a 6−5−5−3 ring-fused structure, was produced in excellent yield. The use of this protocol to obtain a series of analogues of **2u** would produce a new compound library for activity screening. We also investigated ring opening of this ring-fused product. When **2u** was treated with methanol in the presence of catalytic Bu_2SnO, ring opening occurred at the less-strained cyclopentanone moiety rather than at the more-strained cyclopropane moiety, efficiently affording indole carboxylic methyl ester **8u**, which has a 2,2-dicyano-3-methoxycarbonylcyclopropyl group at C-2. It is well-known that ring cleavage, a typical reaction pathway for compounds with small rings, especially cyclopropane and cyclobutane rings, is driven by the release of ring strain.[19] However, methods for cleavage of cyclopentanone derivatives under mild conditions are elusive.[20] The 2,2-dicyano substituted cyclopropane moiety in **8u** contains potentially reactive sites for further synthetic elaboration of this indole-based molecule.[6a,21]

In conclusion, we developed a method for cyclopropanation that is mediated by the water-soluble hypervalent iodine(V) reagent AIBX and that involves dehydrogenation-initiated Michael addition and ring-closure reactions of $C(sp^2)-C(sp^3)$ single bonds in saturated β-ketoesters. This method provides a straightforward, step-economical alternative to the previously reported cyclopropanation strategies, which require substrates bearing at least one C−C double bond. Introducing a chiral ester auxiliary into the substrate led to the efficient synthesis of a cyclopropane bearing two contiguous chiral centers with a high de value. Moreover, this method and further transformation of the products obtained can be expected to facilitate the synthesis of libraries of potentially biologically active compounds. Further scope broadening of this particular cyclopropanation and applying it to modifying complex bioactive molecules are of great significance. Efforts toward these goals are currently ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03209.

Full experimental details; optimization of reaction conditions; characterization data; ORTEP drawing and crystallographic data for compounds **2a** and **2r** (PDF)

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Notes

The authors declare no competing financial interest.

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(10) CCDC 1499164 contains the supplementary crystallographic data for compound **2a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(11) When Dess-Martin reagent and 2-iodoxybenzoic acid were utilized as oxidants, neither gave the desired results, which showed the distinct reactivity of reagent AIBX. For details of optimization, please see the Supporting Information, Section IV.
(12) It was found that using camphorsulfonic acid as the additive instead of AcOH afforded better yields for fully saturated substrates. For details of additive screening, please see the Supporting Information, Section VII.
(13) CCDC 1497797 contains the supplementary crystallographic data for compound **2r**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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