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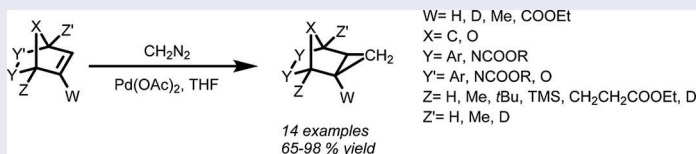
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ABSTRACT

A safer and improved method to our previous report on palladium-catalyzed cyclopropanation of heterobicyclic alkenes has been developed. By using tetrahydrofuran as the solvent and a more dilute aqueous NaOH solution for the generation of diazomethane from Diazald, cyclopropanation could be achieved smoothly with minimal adjustment over the course of reaction. 7-Oxabicyclic substrates with bulky C1 or C2 groups, as well as 2,3-diazabicyclic substrates with various N-substituents, effectively underwent cyclopropanation. Using this methodology, yields to previously reported products were markedly increased, and 10 new cyclopropanated [2.2.1] heterobicyclic products were prepared. In addition, this work accounts for the first reported cyclopropanation of 2,3-diazabicyclic alkenes, which all gave excellent yields of >90%.

GRAPHICAL ABSTRACT

W= H, D, Me, COOEt
X= C, O
Y= Ar, NCOOR
Y'= Ar, NCOOR, O
Z= H, Me, tBu, TMS, CH₂CH₂COOEt, D
Z'= H, Me, D

14 examples
65-98 % yield

Introduction

Cyclopropanes are present in a variety of natural products of plant, fungal, and bacterial origin,[1] and recently their stereoselective synthesis has received much attention in the context of biological activity studies.[2,3] The high ring strain and reactivity of cyclopropanes makes them key intermediates for further transformations and appealing building blocks to more complex structures.[4,5] Numerous methodologies exist for the preparation of cyclopropanated carbobicycloalkenes,[6–11] while the cyclopropanation of heterobicycloalkenes has proved more challenging, with only a limited number of publications to date.[12–14] Inspired by the work of Miller and Ji,[13] our group has recently succeeded in the first Pd(OAc)₂-catalyzed cyclopropanation of 7-oxabenzonorbornadienes, demonstrating

X=H, Me, OMe, F, Ar
Y=H, OMe, F, Br
Z=Me, Et, *n*Bu, *i*Pr, *t*Bu, Br,
C(O)Me, COOMe, CH₂OH
Z'=H, Me
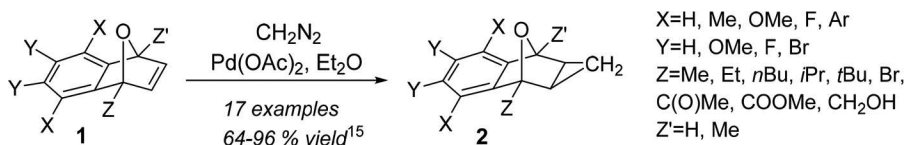
**Scheme 1.** Previously reported cyclopropanations of 7-oxabenzonorbornadienes.

steadfast *exo* stereocontrol of cyclopropanation and broad applicability to variously substituted aromatic and C1-substituted oxabenzonorbornadiene derivatives (Scheme 1).[15] In addition, we have reported on several transformations which these novel systems can undergo.[16,17]

In our previous report on cyclopropanation, however, we were faced with some procedural challenges: namely, the need to supply additional solvent to the reaction vessel during reaction; incomplete consumption of starting material, potentially due to low solubility of the substrate in Et₂O; and minor complications with the addition of a viscous 50% w/v NaOH solution over time. The current work documents a safer and improved procedure to our former cyclopropanation methodology, where the two principle modifications described in this paper are (1) change in reaction solvent and (2) dilution of the aqueous NaOH solution used. In addition, the present work expands the scope of the reaction and introduces the first examples of the palladium-catalyzed cyclopropanation of other [2.2.1] heterobicycles, including 2,3-diazabicyclo-5-heptenes, as well as a hetarene-containing 7-oxabicyclic alkene. The precursor bicycloalkenes that were cyclopropanated in this study were prepared following literature procedures of [4 + 2] cycloadditions between either furans or cyclopentadiene with the appropriate dienophile.[18–23]

Discussion

Upon our attempt to cyclopropanate compound **1d** (Z = tetramethylsilane [TMS], Scheme 2) we found that the substrate did not dissolve well in Et₂O, which was the solvent previously employed for these reactions. Probing the literature, it appeared that the use of other solvents was not uncommon in reactions employing diazomethane.[24,25] After screening the solubilities of substrates in some of these solvents, it appeared that tetrahydrofuran (THF) in fact did a better job of solubilizing several of the alkenes. Use of THF suggested another potential benefit: Because it is higher boiling than Et₂O, evaporation could be minimized and thus periodic addition of solvent by syringe, which could potentially scratch the glassware or expose the chemist to small amounts of gas generated, could be avoided. We also found that by using a more dilute 25% w/v solution and increasing the dropping rate, the addition was smoother and could be left to be monitored less frequently. Accordingly, the glassware dimensions were modified slightly, as well (Figure 3).

These modifications led to improved yields in compounds **2a–c,** which were presented in our former report,[15] as well as successful production of seven new cyclopropanated oxabicycloalkenes **2d–j**, each giving good to excellent yields. The substrates bearing bulky C1-substituents including *tert*-butyl and trimethylsilyl underwent cyclopropanation, providing appreciable yields of 85% and 75% of cyclopropane **2c** and **2d**, respectively. Cyclopropane **2e** with both bridgehead and arene substitution also gave a good yield (82%), as did cyclopropane **2f** with a long-chain bridgehead ethyl ester substituent (81%). Unlike all
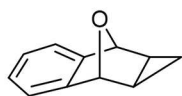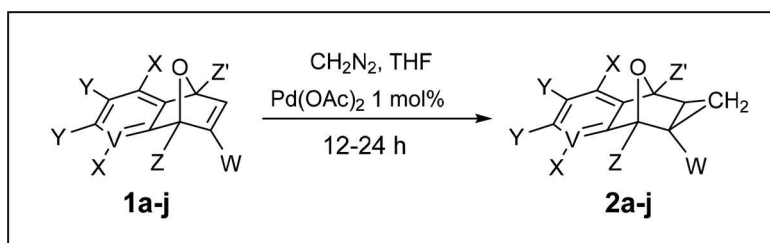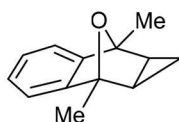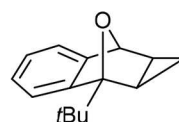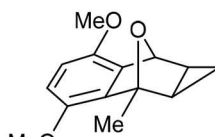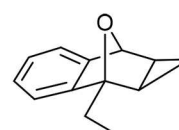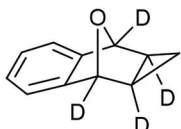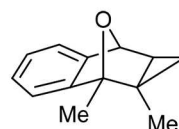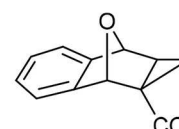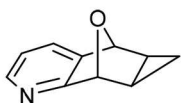
Scheme 2. Cyclopropanation of C1-, C2-, and arene-substituted 7-oxabicycloalkenes **1a–j**. [a]Isolated yields after column chromatography. [b]Isolated yields reported in former study (Et$_2$O solvent).
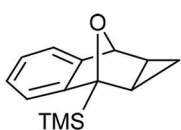
other cyclopropanes, which showed a singlet for bridgehead proton H^a, cyclopropane **2f** showed a doublet at 5.04 ppm with $J = 2.3$ Hz. ^{1}H NMR coupling constants of bridgehead proton H^a to cyclopropyl proton H^b allowed us to deduce the dihedral angle of H^a-C-C-H^b, and the stereochemistry for each cyclopropane (Fig. 1). For the *exo* isomer, J values of 0–2 Hz are expected, whereas for the *endo* isomer a dihedral angle of ~42° and a coupling constant of ~5 Hz is expected.[26–28] The coupling seen in the present study for **2f** is sufficiently close to $J = 2$ Hz that the cyclopropane was concluded to be *exo* with respect to the [2.2.1] bicyclic framework, and this was even more obvious with all other cyclopropanated
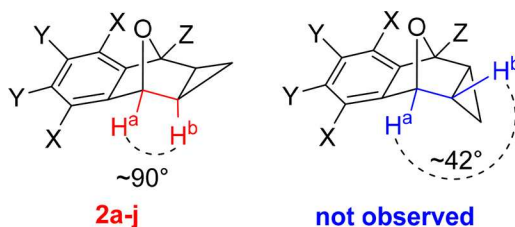
Figure 1. Dihedral angle analysis of *exo* and *endo* cyclopropanes **2a–j**.

oxabicyclics, which showed no observable splitting for the peak of H^a. In addition, tetradeuterated cyclopropane **2 g** was obtained in good yield of 85%, comparable to the undeuterated parent compound **2a**.

Next, cyclopropanations on substituents at the C2-position were attempted, to examine the effect of substituent proximity to the cyclopropanation site. Although both C2-electron-donating and electron-withdrawing substrates **1h** and **1i** required a larger amount of diazomethane for cyclopropanation (6 equivalents for **1h** and 8 equivalents for **1i**), each alkene underwent cyclopropanation to afford the corresponding *exo* cyclopropanated product in desirable yields (94% and 72%, respectively). The yield observed for product **2i** was in good agreement with a known cyclopropanation of a similar C2-substituted 7-oxa-norbornene (lit. 70% for two steps).[14] Finally, substrate **1j** with a fused pyridyl ring also underwent cyc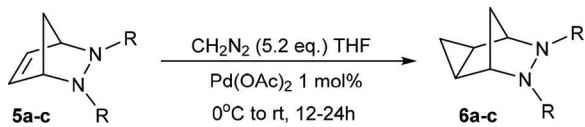lopropanation successfully, suggesting that the scope of this work could be further broadened to other hetarene-containing bicyclic substrates.

By repeating Miller and Ji's cyclopropanation using the current modified conditions on 2-oxa-3-azabicyclic alkene **3**,[13] we were able to reduce both the quantity of diazomethane (from 8 equivalents to 2.6 equivalents) and catalyst loading (from 5 mol% to 1 mol%). Furthermore, we showed that the reaction proceeded equally well in THF as in Et$_2$O (Scheme 3), giving an isolated yield of 97% relative to the previously reported 96%. As there was no precedent of 2,3-diazabicyclic alkene cyclopropanation, we decided to examine these substrates, as well.

Not surprisingly, cyclopropanation of bicyclic hydrazines **5a–c** bearing various N-substituents all gave excellent yields of cyclopropanes **6a–c** (Table 1). Because of the highly fluxional nature of the nitrogen-containing framework of **6a–c**, peaks were broadened with lower intensity in ^{1}H and ^{13}C NMR experiments. Thus, although the presence of ^4J-coupling (W-coupling) between H^a and H^b could not be verified, irradiation of H^c in a selective gradient nuclear Overhauser effect spectroscopy (NOESY) experiment on **6a** unambiguously showed positive enhancement for the peak belonging to $H^{a'}$(as well as for the peak of $H^{c'}$), proving *exo* stereochemistry of the cyclopropane ring (Fig. 2).[29] As with compound **4**, it is conceivable that the products **6a–c** obtained in this work could be ring opened to afford nucleoside derivatives, which are key intermediates for the development of antiviral and antitumor agents.[13]
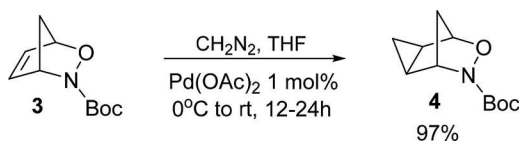
**Scheme 3.** Cyclopropanation of 2-oxa-3-azabicycloalkene **3**.

Table 1. Cyclopropanation of N-substituted bicyclic [2.2.1] hydrazenes **5a–c**.


	Alkene	R	Product	Yield (%)^a
1	**5a**	COOtBu	**6a**	95
2	**5b**	COOiPr	**6b**	94
3	**5c**	COOCH$_2$Ph	**6c**	98

^{a}Isolated yield after column chromatography.

The mechanism of palladium-catalyzed cyclopropanation of alkenes is believed to occur in a stepwise manner,[30] which is consistent with computational work at the B3LYP level of theory.[31] The Pd(OAc)$_2$ precatalyst is reduced to its active Pd(0) state (A, Scheme 4) which then coordinates to the reactant alkene in a bridged η^2 fashion. This initial palladium complex is in equilibrium with the diazomethane-bound intermediate **7**, which releases dinitrogen in a rate-determining step (B). Interaction of a second equivalent of alkene with carbene complex **8** promotes rearrangement to palladacyclobutane **9**, which undergoes reductive elimination (C) to afford the cyclopropane product. In reality, the coordination modes to palladium are thought to be more complex with reversible ligand exchange and largely depend on alkene structure and reaction temperature. Based on Straub's work,[31] it is quite possible that the strained heterobicyclic alkenes in this study react via dialkene carbene complexes (initially coordinated to 2 equivalents of alkene), which later intramolecularly rearrange to palladacyclobutanes **9**.

In conclusion, the present revision of our cyclopropanation methodology was used to create 14 cyclopropanated [2.2.1] heterobicycloalkenes, ten of which were novel compounds and four showing equivalent or improved yields to previous preparations. All cyclopropanes were obtained in good to excellent yields (65–98%) and the *exo* stereoselectivity for each cyclopropane was confirmed through NMR experiments. The current approach offers a safer reaction setup and is applicable to a broad class of heterobicycles, including hetaryne-containing substrates and 2,3-diazenes. Subsequent transformations of the cyclopropanes and expansion of the reaction scope will continue in our laboratories.
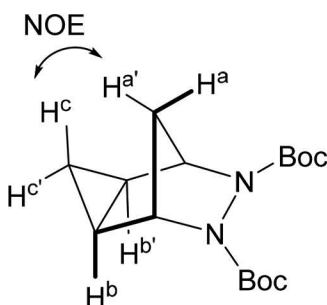
**Figure 2.** Observed NOE correlation for cyclopropane **6a**.
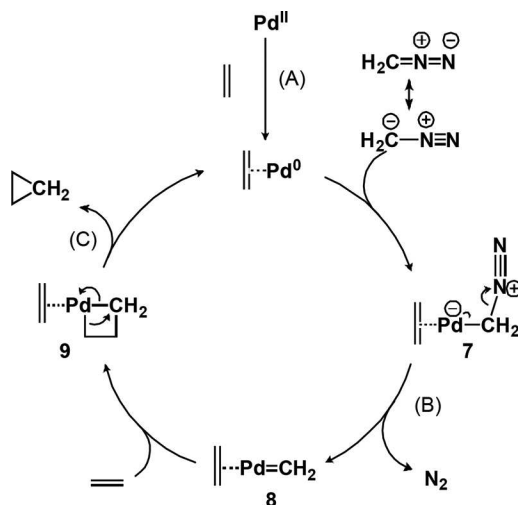
Scheme 4. General mechanism of palladium-catalyzed cyclopropanation of alkenes.

Experimental

All reactions were carried out using a continuous flow apparatus under an inert atmosphere. Commercial reagents and catalysts were used without further purification. Column chromatography was performed on 230- to 400-mesh silica gel following standard flash column chromatography techniques,[32] and analytical thin-layer chromatography (TLC) was performed on precoated silica gel 250 μm 60 F254 aluminum plates, visualized by ultraviolet (UV) light and *p*-anisaldehyde stain. Infrared (IR) spectra were obtained as NaCl or KBr discs on a Nicolet 380-FTIR spectrophotometer. ^1H, ^2H, and ^{13}C NMR spectra were recorded on Avance 400 MHz or 600 MHz spectrometers equipped with cryoprobes and are reported in parts per million (ppm) from the solvent as internal standard [CDCl$_3$: δ 7.24 ppm (^1H at 400/600 MHz) or δ 77.0 ppm (^{13}C at 100/125 MHz)]. HRMS samples were ionized by electron impact (EI) or electrospray ionization (ESI) as specified and detection of the ions was performed by time of flight (TOF).

Cyclopropanated heterobicycloalkenes 1a–j, 4, 6a–c: General procedure

Hazard alert! Diazomethane can be fatal if inhaled and capable of detonation if appreciably concentrated. Refer to Fig. 3: Reactor [C], equipped with a small stir bar; was charged with alkene (1.2–17.7 mmol), Pd(OAc)$_2$ (1 mol% of alkene), and tetrahydrofuran (40 mL); and was capped with septum [E]. To the outlet of reactor [C] was connected in series with Tygon tubing [I] an empty bubbler [J] to serve as a suck-back trap and a glass inlet tube [K] inserted into filter flask [L]. Bubbler [L] was filled prior to setup with a glacial acetic acid–water mixture (1:1). The outlet of bubbler [L] was connected to a piece of Tygon tubing [I$_c$] directed to the back of the fumehood. Reactor [C] was then securely fitted to the end of tube [H$_b$] while cooling its contents in an ice bath. Funnel [A] was filled with 25% (12.5 M) aqueous sodium hydroxide (100–150 equivalents to alkene) ensuring that stopper [D] was tightly shut, and the funnel was capped with septum [E]. Flask [B], equipped with an extralarge stir bar, was charged with Diazald (2.6–8 equivalents to alkene) and 95%
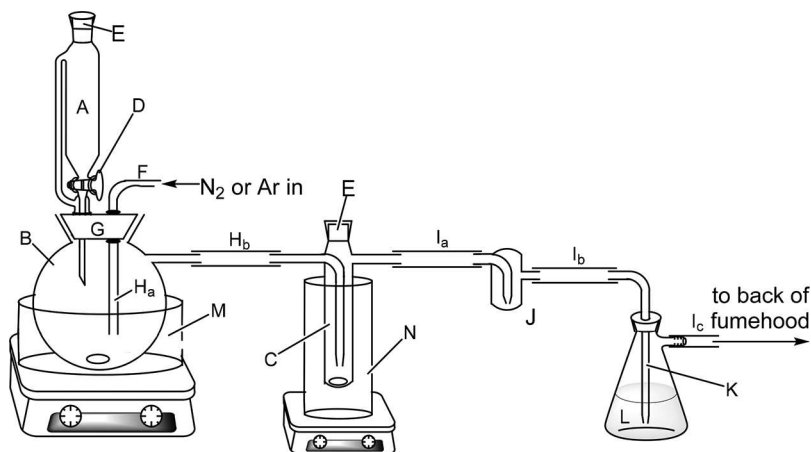
Figure 3. Experimental apparatus for the cyclopropanation of heterobicycloalkenes **1a–j, 3,** and **5a–c.** (A) Custom-made dropping funnel (150 mL or 300 mL). (B) 500-mL round-bottom flask with side arm and wide neck equipped with extra-large stir bar. (C) Reactor vessel (50 mL) with small hole at end of inlet tube for bubbles. (D) Stopcock. (E) Tightly fitted 24/40 rubber septum wired in place. (F) Glass nitrogen/argon inlet (9 mm OD). (G) No. 12 rubber stopper with two 9-mm bored holes. (H) High density polyethylene tubing (7 mm ID) with any cut sharp edges smoothed with a heat gun. (I) Tygon tubing. (J) Empty bubbler as suck-back trap for AcOH bubbler. (K) Glass inlet tube. (L) Filter flask with AcOH:H_2O (1:1) (CH_2N_2 trap and bubbler). (M) Room temperature water bath. (N) 0 °C ice-water bath. *Note.* OD, outer diameter; ID, inner diameter.

EtOH (50 mL), and the solution was stirred. Flask [B] was then fitted with a stopper [G] containing the inert gas inlet [F], tubing [H_a], and addition funnel [A] assembly. The apparatus was securely clamped at both funnel [A] and flask [B] and a slow stream of argon was passed through the system such that ~3 bubbles per second (bps) were observed from tube [H_a]. Once a constant flow rate of 3–5 bps was established, 25% sodium hydroxide solution was added from funnel [A] into flask [B] at a rate of 1–2 mL/min, maintaining efficient stirring and bubbling. Formation of the light yellow CH_2N_2 gas was observed with the dissolution of Diazald. Upon complete dissipation of any yellow color (4–8 h), the reaction was assessed by TLC for completion. Once the reaction was seen to be complete by TLC, both septa [E] were removed and the apparatus was left to vent any trace CH_2N_2 (8–16 h). Reactor [C] was removed and its contents were poured over Celite. The filter cake was washed with several portions (4 × 10-20 mL) of Et_2O, and then concentrated and purified by column chromatography (hexanes/ethyl acetate mixture).

Representative analytical data

Exo-6-oxa-7-N-butoxycarbonyltricyclo[3.2.1.0^{2,4}]hydrazine (6a)

Yield 516 mg (95%); white solid; R_f = 0.08 (EtOAc/hexanes = 1:9); mp = 117–119 °C. FTIR (KBr, ν, cm^{-1}): 2977, 2932, 1737, 1694 (C□O), 1367, 1339, 1164, 1111; ^{1}H NMR (400 MHz, CDCl$_3$): 4.68 (br s, 1H), 4.42 (br s, 1H), 1.59 (m, 1H), 1.43 (s, 18H), 1.31 (d, J=11.3 Hz, 1H), 1.20–1.06 (m, 2H), 0.42–0.39 (m, 1H), 0.33–0.28 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ [156.9, 156.3, 155.3] (C□O; peaks appear split due to relative orientation about nitrogen in different invertomers),[33] [80.2, 80.0], [61.3, 60.4, 59.6], 27.1, 25.8, [13.4, 13.0, 11.6, 11.1], 3.6. HRMS: Calculated for C$_{16}$H$_{26}$N$_2$O$_4$ [M]$^+$: 310.1893. Found: 310.1890.

Funding

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