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RESEARCH ARTICLE

Nickel Nanoparticle-Catalyzed Mono- and Di-Reductions of *gem*-Dibromocyclopropanes Under Mild, Aqueous Micellar Conditions

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Abstract: Mild mono- and di-hydrodehalogenative reductions of *gem*-dibromocyclopropanes are described, providing an easy and green approach towards the synthesis of cyclopropanes. The methodology utilizes 0.5-5 mol % TMPhen-nickel as catalyst that, when activated with a hydride source such as sodium borohydride, cleanly and selectively dehalogenates dibromocyclopropanes. Double reduction proceeds in a single operation at temperatures between 20-45 °C and at atmospheric pressure in an aqueous designer surfactant medium. At lower loading and either in the absence of ligand or in the presence of 2,2'-bipyridine, this new technology can also be used to gain access to not only mono-brominated cyclopropanes, interesting building blocks for further use in synthesis, but also mono- or di-deuterated analogs. Taken together, this base metal-catalyzed process provides access to cyclopropyl-containing products, achieved under environmentally responsible conditions.

Introduction

Improved methods for installation of cyclopropanes onto organic frameworks remain in high demand,[1] as the cyclopropyl moiety can add considerably to a drugs' pharmacological and biological profile.[2] Indeed, cyclopropanes present relatively short, π-character-enhanced C-C bonds as well as shorter and stronger C-H bonds compared to alkanes (106 vs. 101 kcal/mol). They also act as important bioisosteres, replacing phenyl groups as well as olefins during structure activity relationship (SAR) modeling. Just as importantly, such physical properties associated with cyclopropanes can enhance metabolic stability. This observation has sparked development of pharmaceuticals bearing this substructure, and as a result, cyclopropanes can be found in hundreds of APIs as well as in 11 of the 200 top-selling drugs in 2018 (Figure 1).[3] However, most current methods for the direct insertion of the ring rely on precious metal chemistry, requiring stoichiometric quantities of toxic and/or dangerous reagents, along with traditional organic solvents as the reaction medium.[4] Recently, organocatalytic[5] methods, as well as directed evolution and bio-catalysis,[6,7] have provided metal-free alternative processes.

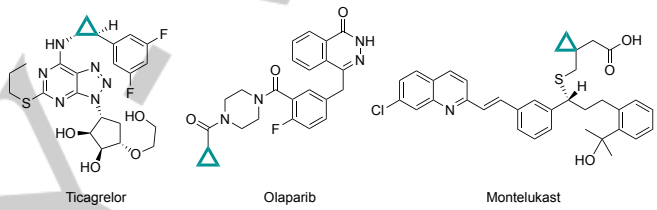

Figure 1. Cyclopropane-containing APIs of current use

Another powerful industrial approach is through initial preparation of *geminal* dihalocyclopropanes, followed by halide removal.[8] Initially developed by Doering and Hoffman,[9] this method involves formation of the cyclopropyl ring through a [2+1] annulation of an olefin and dibromocarbene. Its reliance on inexpensive reagents under ambient conditions represents both a facile and safe process that requires only bromoform as a source of the dibromocarbene, strong inorganic base, and a small amount of phase transfer catalyst. The resulting bromides on the ring can then be reduced to yield the targeted cyclopropane. Reported methods (Figure 2) for such reductions, however, still face serious limitations akin to those that feature direct ring installation; that is, use of stoichiometric, toxic, and dangerous hydride reagents,[10] precious metals with hydrogen pressure,[11]

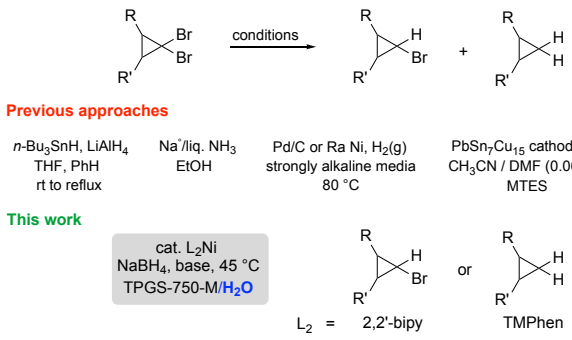

Figure 2. Dibromocyclopropane reductions: comparisons between existing literature methods and newly developed, green approach

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and Birch-type reduction conditions,[12] all of which take place in waste-generating organic solvents.[13] The leading approach, while involving an efficient use of electrochemistry, still relies on organic solvents as well as a substantial amount of organic supporting electrolyte (MTES = *N*-methyl-*N,N,N*-triethyl-ammonium methylsulfate) which may account, in part, for its limited applications to date.[14]

For over a decade, our lab has provided environmentally responsible technologies involving nanoparticles that function as nanoreactors, formed from "designer" surfactants. These nanomicelles enable catalysis in water under mild (usually, room temperature) conditions. The ability to run organic reactions in an aqueous medium,[15] rather than in organic solvents, dramatically reduces the environmental impact associated with organic synthesis, as typified by comparisons of E Factors.[16,17] Along the way, we have also explored the opportunity of running gas-evolving reduction reactions in aqueous micellar media, resulting in a broad portfolio of reductive reactions using nanoparticles (NPs).[18,19] Herein, we report the use of catalytic amounts of new nickel NPs that function as a catalyst for the reduction of *gem*-dibromocyclopropanes in aqueous solutions of TPGS-750-M, in the presence of $NaBH_4$ as the source of hydride (Figure 3). The tuning of conditions also allows access to mono-brominated cyclopropanes, building blocks that allow for further derivatization.

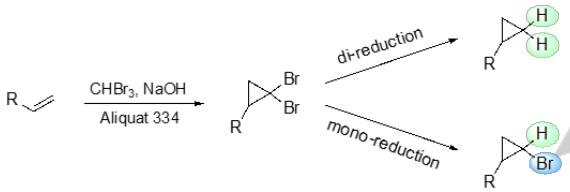

Figure 3: Formation of gem-dibromocyclopropanes followed by mono- or di-reduction

Results and Discussion

As previously reported,[20] use of zinc to simultaneously reduce both bromides was challenging; a mixture of mainly mono-reduced and di-reduced products were observed when using commercially available zinc metal. In evaluating nickel boride chemistry,[21] we began with inexpensive and readily available $Ni(OAc)_2{\cdot}4H_2O$, as well as with $NaBH_4$ as the terminal reductant. The impact of the ligand was extensively screened, and as expected, played a major role in the outcome of these reductions (Table 1). When 5 mol % of the nickel source was used with no ligand (entry 1), the starting material **1** was completely consumed, leading to an easily separable mixture (88:12) of mono- and the di-reduced cyclopropane, respectively. To favor double reduction, 3,4,7,8-tetramethyl-1,10-phenanthroline (TMPhen) was screened using different ratios relative to nickel (5 mol %): 1:1 (entry 2), 2:1 (entry 3) or 3:1 (entry 4). In each case, significant gas evolution was observed. The combination of 10 mol % ligand (2:1 ratio to Ni) afforded the corresponding di-reduced cyclopropane in 91% isolated yield. Increasing the amount of ligand significantly slowed the reaction, yielding a mixture of the mono- and di-reduced product. To ensure that $NaBH_4$ was not partially responsible for the reduction, a reaction in the absence of catalyst returned only starting material (entry 5). With the optimized ligand/metal ratio, other ligands were also investigated (entries 6-9).

Interestingly, other phenanthroline-based ligands led to a larger proportion of the mono-reduced over di-reduced cyclopropane, in all cases with complete loss of educt. Reducing the amount of catalyst to 0.5 mol % and introducing 2,2'-bipyridine (bipy) as the ligand at 1.0 mol % (entry 11) provided access to primarily the mono-brominated product, with some di-reduced material being detected. Pursuing the reaction using only nickel(II) salts activated by sodium borohydride without ligand gave the highest selectivity for the mono-brominated product (see Table **1**, entry 10). However, further studies found that the 2,2'-bipyridine ligand was required for full consumption of the starting materials when the complexity of the starting di-halogenated substrate is increased.

The optimal amount of hydride for double reduction was also determined (Table 2). In an initial screening, five equivalents of $NaBH_4$ led to compound **2** in 77% isolated yield. Reducing this amount led to poorer yields (entries 1-3). In presence of 20 v/v % of THF, the yield was increased to 91% (entry 5). Replacing $NaBH_4$ by KBH_4[22] was of no consequence (entry 6).

The base was also evaluated (see SI, Table S1), with both pyridine and 2,6-lutidine found to be optimal candidates for these reactions. Nevertheless, adding base before or after NP formation did not affect the reaction outcome. The reaction medium played an important role in the efficiency of the system. While water only (Table 3, entry 1) was suitable for compound **1** leading to **2** in 79% yield, more lipophilic substrates gave low levels of conversion in this medium. The addition of 20 v/v % of THF increased the yield of **2** to 86% (entry 2). However, attempted reduction of compound **4** to product **5** in a similar aqueous medium (80:20 H_2O/THF) led to no conversion (entry 3). Likewise, the reaction run in pure THF failed (entry 4).

In order to improve conversions with more lipophilic substrates, the choice of surfactant was investigated. Addition of 2 wt % Triton X-100, Nok,[23] or TPGS-750-M led to mixed results, where only Triton X-100 and TPGS-750-M matched the results obtained in water only. The yield with TPGS-750-M was slightly higher in presence of 20 v/v % of THF, leading to the best results. Applications to other substrates showed a significant improvement due to the presence of an amphiphile. Indeed, compound **5** was obtained in 72% isolated yield using 2 wt % of TPGS-750-M in water + 20 v/v % of THF (entry 9). Other protic solvents such as ethanol are not recommended as a violent reaction took place (entry 11). To our surprise, reversing the organic to aqueous ratio (entry 10), i.e., 80% THF / 20% aqueous surfactant resulted in nearly quantitative yield of product **2**. A similar yield increase was also observed for reduction of dibromide **4**, giving 77% of the doubly reduced product **5**. However intriguing, this line of research was not explored further because of the unsustainable status of bulk organic solvents in chemical synthesis.

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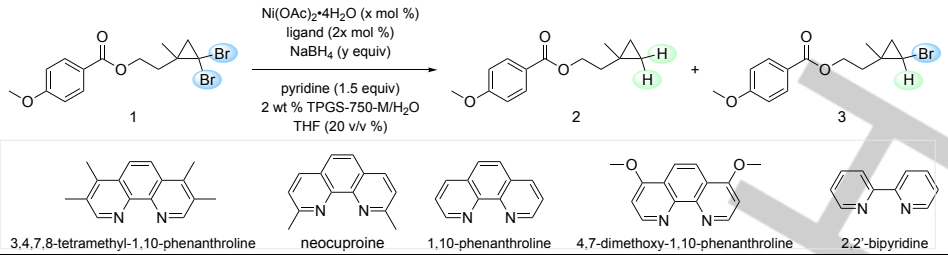
Table 1. Screening of ligands to optimize bromocyclopropane reductions



Entry	Catalyst (mol %)	Ligand (mol %)	$NaBH_4$ (equiv)	Ratio of **1** / **2** / **3**[a]
1	$Ni(OAc)_2•4H_2O$ (5)	/	5	0 / 12 / 88
2	$Ni(OAc)_2•4H_2O$ (5)	3,4,7,8-tetramethyl-1,10-phenanthroline (5)	5	0 / 100 (82)[b] / 0
3	**$Ni(OAc)_2•4H_2O$ (5)**	**3,4,7,8-tetramethyl-1,10-phenanthroline (10)**	**5**	**0 / 100 (91)[b] / 0**
4	$Ni(OAc)_2•4H_2O$ (5)	3,4,7,8-tetramethyl-1,10-phenanthroline (15)	5	0 / 77 / 23
5	/	---	5	100 / 0 / 0
6	$Ni(OAc)_2•4H_2O$ (5)	neocuproine (10)	5	0 / 20 / 80
7	$Ni(OAc)_2•4H_2O$ (5)	1,10-phenanthroline (10)	5	0 / 19 / 81
8	$Ni(OAc)_2•4H_2O$ (5)	4,7-dimethoxy-1,10-phenanthroline (10)	5	0 / 10 / 90
9	$Ni(OAc)_2•4H_2O$ (5)	2,2'-bipyridine (10)	5	0 / 13 / 87
10	**$Ni(OAc)_2•4H_2O$ (0.25)**	**---**	**2.5**	**0 / traces / >99**
11	**$Ni(OAc)_2•4H_2O$ (0.5)**	**2,2'-bipyridine (1)**	**2.5**	**0 / 3 / 97**

[a] Determined from analyses of crude material by ^1H NMR; [b] Results in parentheses refer to isolated yields.

Double reduction was optimal using 5 mol % of $Ni(OAc)_2·4H_2O$ and 10 mol % TMPhen in the presence of five equivalents of $NaBH_4$, and 1.5 equivalents of pyridine, run in 2 wt % of TPGS-750-M/H_2O containing 20 % v/v of THF. Reducing the amount of catalyst to 1 mol % was sufficient for some substrates but, unfortunately, this level of Ni was found not to be generally applicable. Mono-reduction could be performed in this aqueous medium using only 0.5 mol % of the same $Ni(OAc)_2·4H_2O$, in the presence of 1 mol % of the ligand 2,2'-bipyridine and 2.5 equivalents of $NaBH_4$.

Table 2. Impact of the amount of $NaBH_4$

entry	$NaBH_4$ (equiv)	yield (%)[a]
1	2	19
2	3	70
3	4	71
4	5	77
5	5	91[b]
6	5	91[b],[c]

[a] isolated yields; [b] in presence of 20 v/v % THF; [c] KBH_4 instead of $NaBH_4$

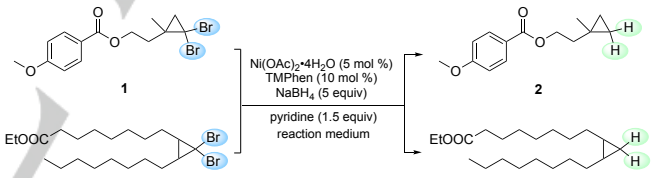


Table 3. Screening of the reaction medium for educts **1** and **4**

entry]	SM	medium	co-solvent	yield (%)[a]
1	**1**	water	---	79
2	**1**	water	THF (20 v/v %)	86
3	**4**	water	THF (20 v/v %)	0
4	**1**	THF	---	0
5	**1**	2 wt % Tritron X-100/H_2O	---	76
6	**1**	2 wt % Nok/H_2O	---	44
7	**1**	2 wt % TPGS-750-M/H_2O	---	77
8	**1**	**2 wt % TPGS-750-M/H_2O**	**THF (20 v/v %)**	**91**
9	**4**	2 wt % TPGS-750-M/H_2O	THF (20 v/v %)	72
10	**1**	**THF**	**2 wt % TPGS-750-M/H_2O (20 v/v %)**	**99**
11	**1**	EtOH	---	---[b]

[a] Isolated yields of either products **2** or **5**; [b] A violent reaction ensued

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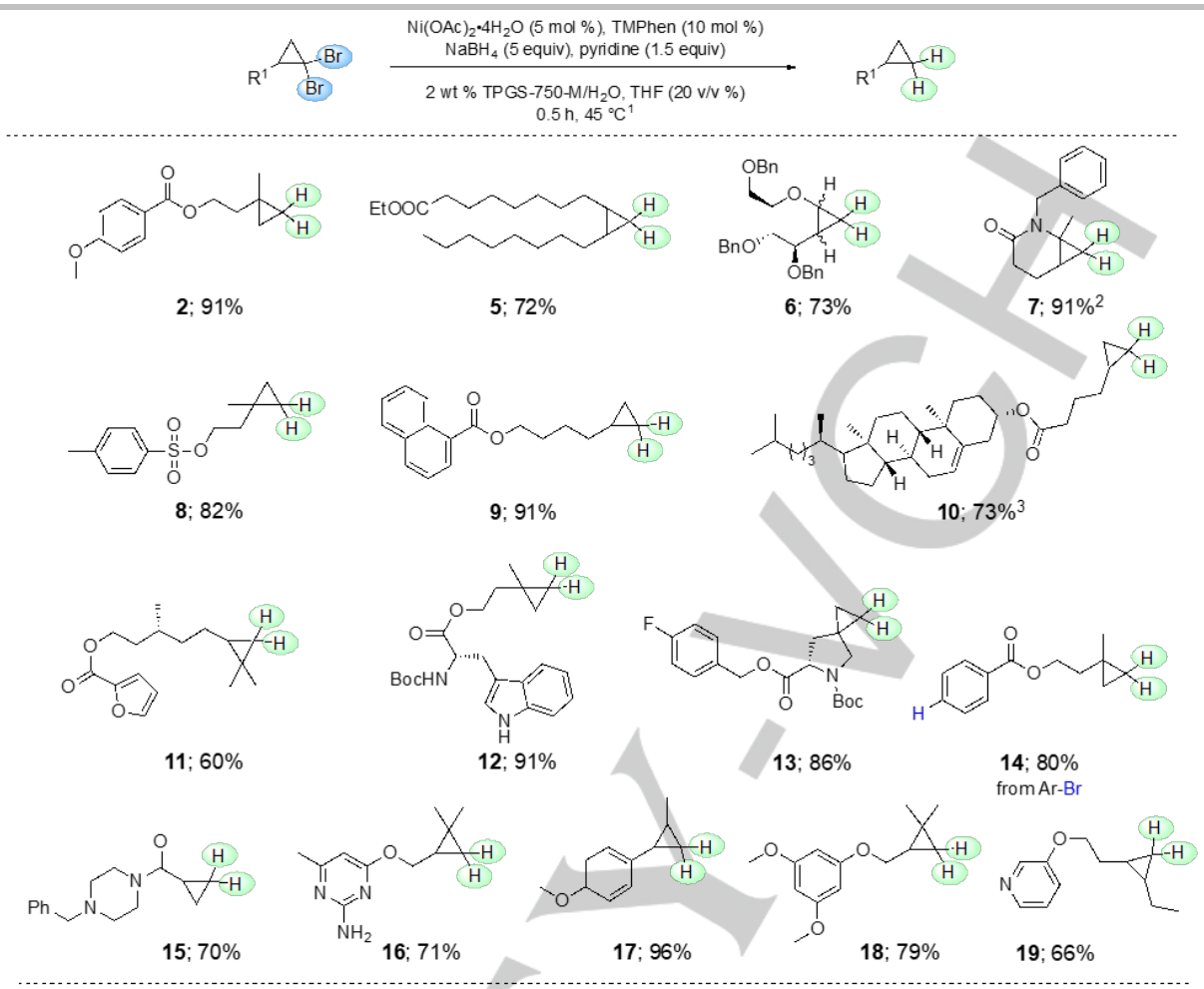

[1]Isolated yields; [2]Performed at rt; [3]50%TPGS-750-M/H_2O, 50% THF.

Figure 4. Scope of di-reduction of 1,1-dibromocyclopropanes

With these optimized conditions, the scope of both di- (Figure 4) and mono- (Figure 5) reductions could be evaluated. Moderate-to-high yields were obtained with variously functionalized dibromides. Fused rings, important structures found in natural products, are tolerated, as shown for compounds **6** and **7**. Given their sensitive nature, reactions at room temperature were found to be optimal. The presence of a tosylate is also well tolerated, as illustrated by product **8**. Ethyl dihydrosterculate **5**, an ester of the natural product acid precursor, was prepared from the corresponding *gem*-dibromocyclopropane (72%). Unlike methods involving $LiAlH_4$,[24] the ester functionality remained unaffected by these reducing conditions, as exemplified further by **9**. The reaction was well tolerated by a cholesterol derivative leading to **10** in 73% yield without any observed reduction of the trisubstituted olefin. Best results to arrive at **10** were observed when the reaction was run with a 1:1 mixture of surfactant solution and THF. However, running this reaction under pressure in a sealed vial allows the reaction to take place with 20 v/v % THF resulting in 60% yield. Heteroaromatic compounds, including the furan-based compound **11** and indole **12**, were obtained in 60% and 91% yields, respectively. Compound **13**, a protected analogue of an API building block, could be prepared in 86% yield.[11] A somewhat larger scale reaction en route towards **13** (1.52 mmol; 0.77 g) afforded the targeted product in 78% isolated yield (0.41 g).

Nitrogen-containing heterocycles formed a N→BH3 complex that can be liberated with an acidic workup of hydrochloric acid in methanol at pH <1 prior to quenching with aqueous sodium bicarbonate solution. The reaction has been found to work under atmospheric pressure and, while being run in an open flask led to no conversion, keeping the flask under argon pressure is not necessary. The reaction need only be kept under light pressure developed by decomposition of excess sodium borohydride producing hydrogen gas, using a syringe with plunger to monitor gas evolution. Unfortunately, starting from *gem*-dichlorocyclo-propanes is not a viable path, as only 7% conversion was observed from the analogous version of compound **1**.

Monobromocyclopropanes were also successfully synthesized from a selection of previously prepared *gem*-dibromocyclopanes, as illustrated in Figure 4 (see conditions developed in Table 1). Excellent yields were obtained for the five examples studied, including the reduction of **1** to **3** (91% yield). Note that mono-reduction leading to **23** corresponds to the monobromide of API intermediate **13**. Recent literature provides an alternative, direct route to mono-bromocyclopropanes from olefins using catalytic chromium, bypassing dihalocyclopropane intermediates.[25] The method disclosed herein, however, avoids highly toxic metals and associated use of organic solvents, while yields of the mono-brominated products prepared in water remain high throughout this 2-step process.

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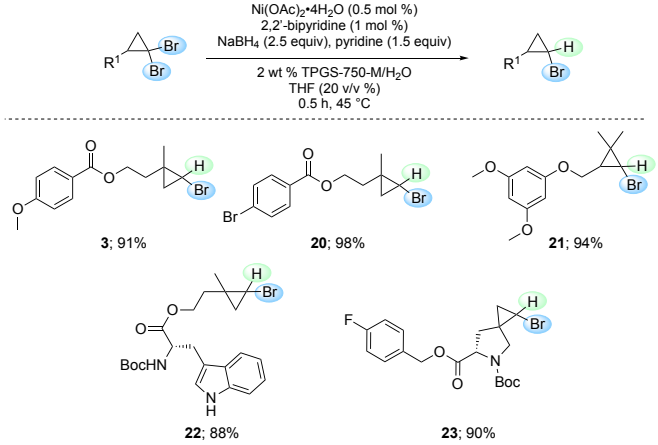

Figure 5. Scope of mono-reduction of 1,1-dibromocyclopropanes

Using educt **24** as a model system (Figure 6), different outcomes have been observed under mono- or di-reduction conditions. Both the *gem*-dibromocyclopropane and the aryl bromide were reduced using Ni/TMPhen di-reduction conditions, while the latter remained unaffected under mono-reduction conditions, giving access to **20** in 98% yield.

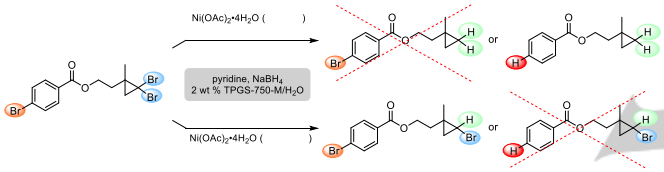

Figure 6. Mono- and di-reduction of substrate **24**

A tandem, 1-pot process involving an initial ppm Pd-catalyzed[26] Suzuki-Miyaura cross-coupling could be performed given the same aqueous micellar conditions characteristic of both reactions (Figure 7). Thus, cyclopropane-containing biaryl **25** could be accessed via **24** in an overall isolated yield of 86%. This further highlights the robustness of this method, which tolerates the presence of residual salts and catalysts from the previous step.

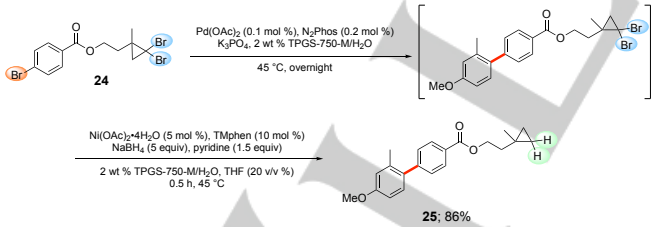

Figure 7. Tandem Suzuki-Miyaura/*gem*-dibromo reduction in 1-pot

As testimony to the greenness of this process, the reaction medium has been recycled three times with no significant loss of reactivity (see SI). Moreover, the associated E Factor for the conversion of **1** to **2** has been calculated to be 5, including extractions of the aqueous reaction medium with EtOAc (see SI). Importantly, ICP-MS analysis of product **2** following double reduction and a standard workup indicated that <2 ppm nickel was present (Figure 8) which is far below the FDA allowed level for nickel/dose.[27]

Insofar as the mechanism(s) associated with both mono- and di- reductions, initial reactions focused on reduction to the mono-bromide. Starting material **1** was treated with various reagents, including reductants ($NaBH_4$ vs. $NaBD_4$), co-solvents (THF vs.

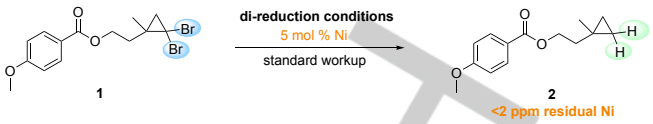

Figure 8: Less than 2 ppm residual nickel in product after standard workup procedure

THF-d_8), base (pyridine vs. pyridine-d_5), and the bulk aqueous medium (H_2O vs. D_2O; Figure 9). Interestingly, use of sodium borodeuteride, while holding all other reagents of the reaction constant (as non-deuterated species) resulted in only 18% of the mono-deuterated bromo-cyclopropane (**26**) via NMR analysis of the crude reaction mixture. Reduction in the presence of THF-d_8 or pyridine-d_5 with $NaBH_4$ as hydride source led to only trace amounts of the deuterated species. Likewise, running the reaction in D_2O resulted in no deuterium incorporation.

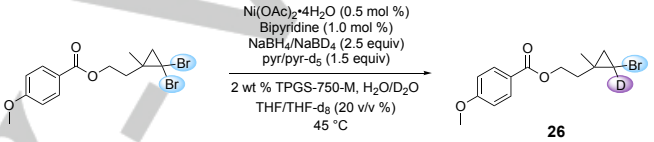

Figure 9. Cyclopropane deuteration under mono-reduction conditions

Screening of several permutations of deuterated reagents under micellar conditions gave the mono-deuterated product in yields of 30-84% (see SI). Highest levels of deuterium incorporation arose when all reagents were in deuterated form. Curiously, removing TPGS-750-M entirely from the reaction medium, in the presence of deuterated reagents, led (albeit in lower yield) to nearly quantitative deuterium incorporation. This suggests that hydrogen atoms likely available from this surfactant via a radical chain mechanism effectively compete with all other sources of deuterium. Holah *et al*., noted that Ni(II) salts ligated in a 1:2 ratio to 2,2'-bipyridine or phenanthroline ligands and activated by sodium borohydride led to a Ni(I) species with empirical formula $Ni(ligand)_2BH_4•2H_2O$, which may then quickly form the active borane radical anion, explaining the fast reaction we observe.[28] On the other hand, use of this reagent as reported (ligand = Phen) under these conditions (e.g., see Fig. 3) with educt **1** afforded a 62:38 mix of the corresponding mono- or doubly-reduced cyclopropane (Table 1, entry 7).

Further reduction of **3** was found to be prohibitively slow under mono-reduction conditions, thus leading to high selectivity for the mono-bromo product **3**. Subjecting **3** to di-reduction conditions, however, quickly results in formation of the di-reduced cyclo-propane (**27**). Deuteration using only sodium borodeuteride under the di-reduction conditions (Figure 10) results in quantitative deuterium incorporation on the cyclopropane ring, suggesting that

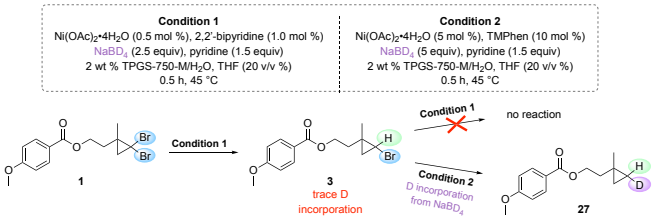

Figure 10. 2-Step process towards fully reduced, mono-deuterated product **27**

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the second bromide is reduced via a different mechanism than that involved in mono-reduction of **1**.

Deuteration under di-reduction conditions was further explored by subjecting a *gem*-dibromocyclopropane to a similar set of permutations of deuterated reagents, as in the mono-reduction condition case (see SI). All experiments run under these conditions resulted in complete dehalogenation of the cyclopropyl ring. A mixture of mono- and di-deuteration products was observed by NMR analysis of crude reaction mixtures in the case where sodium borodeuteride was used together with THF-d_8 or D_2O. However, the combination of all three deuterated reagents resulted in clean di-deuteration product (**28**) (Figure 11). Only a trace, if any, of monobromocyclopropane product **26** is observed by GCMS analysis of the reaction at any time point.

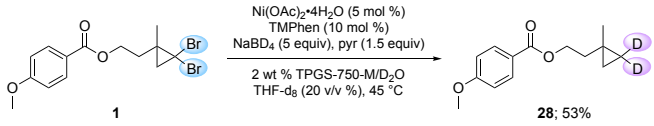
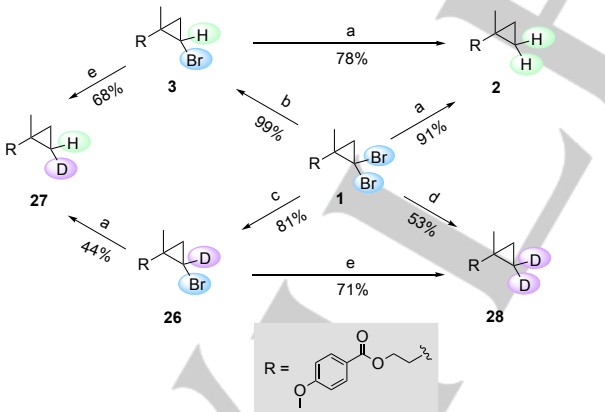


Figure 11. Direct di-deuteration of *gem*-dibromocyclopropanes

With conditions for either mono- or di-deuteration in hand, options for arriving at partially or fully debrominated cyclopropanes, originating from the same *gem*-dibromocyclopropane **1**, are summarized in Figure 12. Reactions leading to deuterated products, whether of a mono- or di-deuterated nature, afford noticeably lower isolated yields relative to those that form protiated species (i.e., see **26**, **27**, and **28** vs. **2** and **3**; Figure 11). This is expected based on prior art describing such a nuclear isotope effect wherein (in the absence of an activating transition metal) sodium borohyride/borodeuteride resulted in a k_H/k_D of 4.4 for mono-reduction.[29] Interestingly, synthesis of compound **2** from **1** gives a significantly lower yield for the overall 2-step process (77% via **3**) compared to the 1-step direct double



a) $Ni(OAc)_2$•$4H_2O$ (5 mol %), TMPhen (10 mol %), pyridine (1.5 equiv), and $NaBH_4$ (5 equiv) in 2 wt % TPGS/H_2O (20 v/v % THF).

(b) $Ni(OAc)_2$•$4H_2O$ (0.5 mol %), BiPy (1.0 mol %), pyridine (1.5 equiv), and $NaBH_4$ (2.5 equiv) in 2 wt % TPGS/H_2O (20 v/v % THF).

(c) $Ni(OAc)_2$•$4H_2O$ (0.5 mol %), BiPy (1.0 mol %), pyridine-d_5 (1.5 equiv), and $NaBD_4$ (2.5 equiv) in 2 wt % TPGS/D_2O (20 v/v % THF-d_8).

(d) $Ni(OAc)_2$•$4H_2O$ (5 mol %), TMPhen (10 mol %), pyridine (1.5 equiv), and $NaBD_4$ (5 equiv) in 2 wt % TPGS/D_2O (20 v/v % THF-d_8).

(e) $Ni(OAc)_2$•$4H_2O$ (5 mol %), TMPhen (10 mol %), pyridine (1.5 equiv), and $NaBD_4$ (5 equiv) in 2 wt % TPGS/H_2O (20 v/v % THF).

Figure 12. Methodologies developed herein for accessing various substitution patterns in a water/THF mixture

dehalogenation (91%). In all cases, separation of the doubly reduced cyclopropane product from either the mono-reduced, or dibrominated starting material, if needed, was found to be quite straightforward.

Conclusions

A new, general technology has been developed that allows for the direct conversion, via Ni catalysis, of readily available *gem*-dibromocyclopropanes to their doubly reduced cyclopropanes. Alternatively, mono-reduction to the corresponding monocyclopropyl bromide using related Ni catalysis is another available option, as is entry to either mono- or di-deuterated cyclopropyl analogs. Under the reported conditions, direct application to a spirocyclic API intermediate has been demonstrated. Overall, this approach relies on typical reaction facilities, requiring no special equipment, and is environmentally attractive in that it takes place in recyclable water under mild conditions, enabled by small amounts of an environmentally benign and commercially available amphiphile.

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Keywords: reductions of bromocyclopropanes • micellar catalysis • chemistry in water • nickel nanoparticles • catalysis

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Two for the price of one. Double reduction of *gem*-diboromcyclopropanes, done in 1-pot in recyclable water and with base metal, Ni, catalysis, leads to the corresponding cyclopropanes. This new technology is tolerant of several functional groups, can be modified to allow for mono-reduction, including mono- or di-deuteration. Residual levels of Ni in the products tend to be <2 ppm.

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