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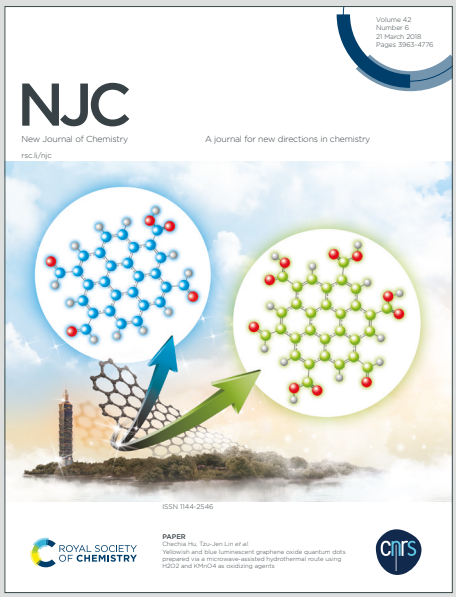

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A Comparative Study of Thallium(III) and Iodine(III)-Mediated Ring Contraction Reactions for the Synthesis of Indane

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Reported herein, is a comparative study for the synthesis of indane via ring contraction reaction, mediated by iodine(III) and thallium(III). A series of protected 1,2-dihydronaphthalenes were synthesized, and subjected to hydroxy(tosyloxy)iodobenzene (HTIB) and thallium(III) nitrate trihydrate (TTN) in trimethyl orthoformate (TMOF) to compare the percent yields provided by both oxidizing agents. The yields of the ring contracted products (indanes) were in the range of 61-88% for reactions performed with TTN.3H_2O in TMOF. However, these yields were recorded significantly lower (e.g., 18-34%) while used HTIB in TMOF with some addition products. This study provides an important development related to the efficacy of two oxidizing agents for ring contraction reaction.

Keywords: ring-contraction, iodine(III), thallium(III), 1,2 dihydronaphthalenes, indanes

Introduction.

Indanes, also known as benzocyclopentanes, and its derivatives, display important biological activities, including anti-allergic, anti-tumor, anti-convulsant, anti-hypercholesterolemic, herbicidal, fungicidal and antimicrobial activities.[1] Indane derivatives also have numerous applications in the fields of material science and nanoscience.[2] Moreover, indane moieties are important constituents of many natural products[3–7] and comprise the backbone of various potential therapeutic agents.[8–10] **Scheme 1** summarizes the efficient synthetic approaches, reported by various authors for the development of indane-based natural products.[1] These include but not limited to intramolecular Friedel-Crafts-type cyclization reactions,[11] cycloaddition reactions,[12] cyclization involving Michael-type addition reactions,[13] cyclization involving Heck-type reactions,[14,15] Prins-type reactions [16] and ring contraction reaction of tetralones via TI(III) or I(III).[17]

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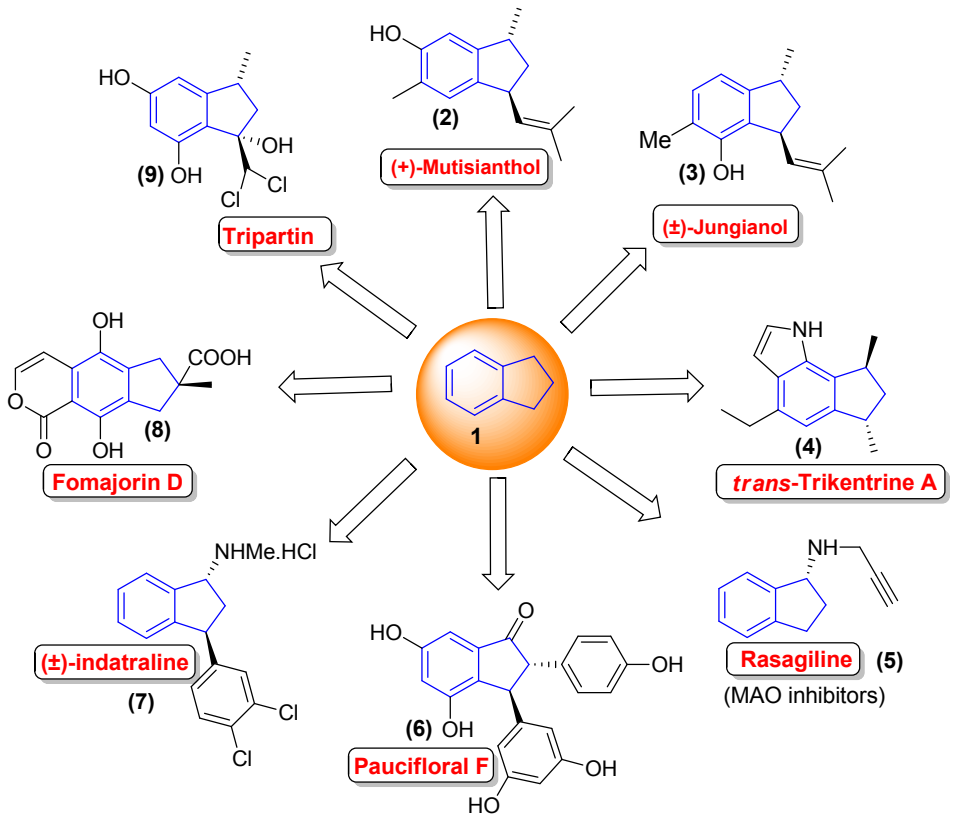
The oxidative rearrangement of six-membered carbocycles into indanes is a promising, versatile and efficient strategy.[18]

Thallium(III) and iodine(III) are the two effective and practical oxidizing agents. Both oxidants have some similar but interesting synthetic applications in organic chemistry. For example, both of these agents are in cyclization of alkenols,[19,20] phenolic oxidative coupling,[21,22] oxidative rearrangement,[23–25] and readily reacts with phenols,[26] or nitrogen of the indoles.[25,27] However, the scope of commercially available TTN-mediated ring contraction reactions involving cyclohexane derivatives is relatively well-explored.[28–30] In recent years, the conversion of 1,2-dihydronaphthalene and its derivatives to the corresponding indane products (benzocyclopentanes) via treatment with thallium salt (TTN) in suitable solvents have been extensively studied by Dr. Silva, Jr. group.[31–33] For example, the total synthesis of phenolic sesquiterpene (±)-mutisiantol (**2**) was performed via the rearrangement of the corresponding 1,2-dihydronaphthalene substrate using thallium(III) in TMOF. The resulting indane was isolated in 94% yield. This reaction was the key step in both the racemic as well as in the asymmetric synthesis of mutisianthol (**2**).[34,35] Similarly, the chemoselectively total synthesis of an antimicrobial alkaloid, *trans*-trikentrin A (**4**), was accomplished by using TTN.[36]



Scheme 1. Indane-based natural products and their analogues.

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Apart from the synthetic application, thallium has strong application nature in industry such as semiconductor production, optical glasses, alloys, photoelectric cells, radioisotopes, etc.[37] Despite the importance of thallium, the toxicity of thallium salts for aquatic life has raised interest for safer alternatives.[38,39] In this direction, hypervalent iodine reagents were developed as an environmentally benign alternative and drawn intense interest from chemists during the last two decades.[40–43]

HTIB (hydroxy-(tosyloxy)iodo]benzene or Koser's reagent) has been found to be an efficient tool for promoting ring contraction reaction.[44,45] Several articles describe the synthesis of indanes through HTIB-promoted ring contraction reactions.[17,46,47] For instance, (±)-Indatraline (**7**) is a potent drug capable of counteracting the effects of cocaine. The diastereoselective total synthesis of (±)-indatraline (**7**) using ring contraction reaction with HTIB in MeOH has been developed as the vital step.[10] As the choice of solvent has great importance in these rearrangement reactions. For example, acetal formation has been observed with the use of nucleophilic solvents such as TMOF, EtOH, MeOH, or TFE (2,2,2-trifluoroethanol).[48]

In this study, we are here describing a comparative study for the synthesis of indane via ring contraction reaction, mediated by iodine(III) and thallium(III). A series of various protected 1,2-dihydronaphthalenes were subjected to HTIB and TTN in TMOF under similar reaction conation, to compare the yields. To the best of our knowledge, no prior research has reported to compare iodine(III) and thallium(III) mediated ring contraction reactions for the same substrate. Moreover, various protecting group were introduced to the substrates, aim to study the protection group tolerance for both oxidizing agents. Therefore, this study provides significant development about the two oxidizing reagents in terms of effectiveness for ring contraction reactions.

Results and discussion.

To study ring contraction reaction for the synthesis of indane skeleton, a series of 1,2-dihydronaphthalenes bearing various substituents were prepared (see Supporting Information) followed by their treatment with HTIB and TTN in TMOF to compare the reactivities as well as the yields of both oxidative agents. These results are summarized in **Tables 1** and **2**. Compound **14a** was treated with HTIB in TMOF and the resulting acetal product was isolated in 29% yield (**Table 1**, entry 1). Previously, poor yields in MeOH or TMOF for reactions involving methoxy-substituted 1,2-dihydronaphthaline compounds was reported.[48] The low yield of the ring-contracted product can likely be attributed to the electron-donating effect of the methoxy group, which increases the reactivity of the cationic intermediate produced by the iodine(III) species, thus causing the formation of byproducts some.[48]

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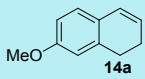
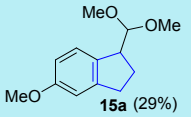
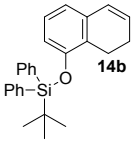
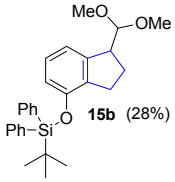
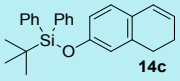
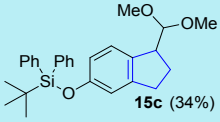
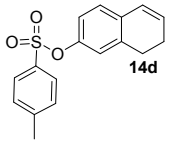
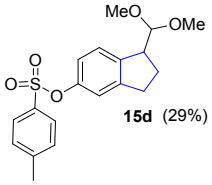
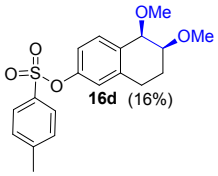
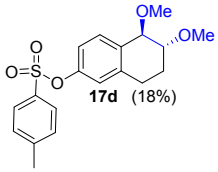
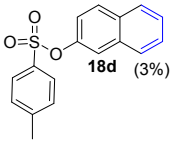
In subsequent reactions, the electron-donating effect was decreased via the introduction of protective groups such as *t*-butyldiphenylsilyl *meta* and *para* to the migratory carbon of the ring. Compounds **14b** and **14c** reacted with HTIB in TMOF forming the corresponding acetals **15b** and **15c**, in 28% and 34% yields, respectively (Table 1, entries 2 and 3). The reaction of tosyl- and 2,4,6-trimethylbenzoyl-protected alkenes (**14d** and **14e**) with HTIB in TMOF gave four distinctive products. Tosyl-protected alkene **14d** led to the ring contraction product **15d**, in 29% yield, the *cis*-addition product **16d**, in 16% yield, the *trans*-addition product **17d**, in 18% yield, and the aromatized product **18d**, in 3% yield (entry 4). Similarly, alkene **14e** led to the ring-contracted product **15e**, in 31% yield, the *cis* addition product **16e**, in 15% yield, the *trans* addition product **17e**, in 17% yield, and the aromatized product **18e**, in 4% yield (**Table 1**, entry 5).

The dimethoxy 1,2-dihydronaphthalene compound **14f** was also treated with HTIB that gave the corresponding indane in 18% yield with two addition byproducts of (*cis*- and *trans*) and an aromatic product (Table 1, entry 6). The HTIB-mediated oxidation of benzamide **14g** was monitored by TLC analysis, which showed four spots, but only the ring contraction product **15g** and *trans*-addition product **17g** could be isolated in 32% and 19% yields, respectively (Table 1, entry 7).

Table 1 HTIB-mediated ring contraction reactions in TMOF.

Entry	Substrate	Acetal (Indane)	Addition product (*cis*)	Addition product (*trans*)	aromatization
1	 **14a**	 **15a** (29%)	***	***	***
2	 **14b**	 **15b** (28%)	***	***	***
3	 **14c**	 **15c** (34%)	***	***	***
4	 **14d**	 **15d** (29%)	 **16d** (16%)	 **17d** (18%)	 **18d** (3%)

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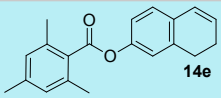
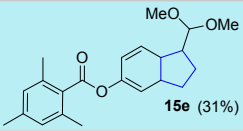
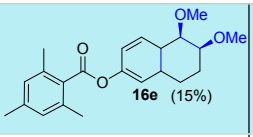
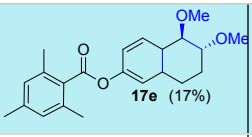
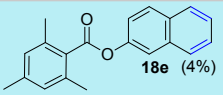
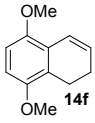
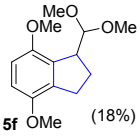
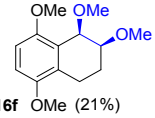
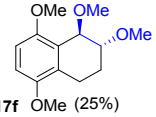
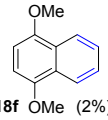
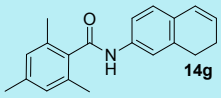
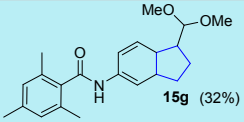
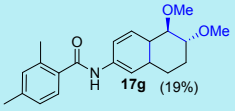
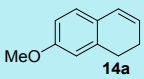
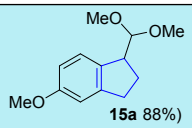
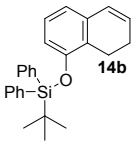
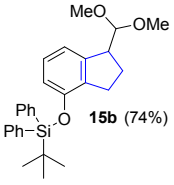
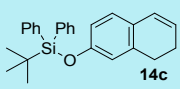
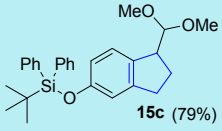
5	 **14e**	 **15e** (31%)	 **16e** (15%)	 **17e** (17%)	 **18e** (4%)
6	 **14f**	 **15f** (18%)	 **16f** (21%)	 **17f** (25%)	 **18f** (2%)
7	 **14g**	 **15g** (32%)	***	 **17g** (19%)	***

*** = *Compounds analyzed by TLC but could not characterized due to their low yields.*
Reaction conditions: *1.2 equiv HTIB, TMOF, rt, 5 min*

Our data clearly supports that HTIB-mediated oxidation of alkenes in TMOF gave the corresponding acetals as major products but with low yields (28-34%), except for **14f**. However, these yields were considerably improved when iodine(III) was replaced with thallium(III) in TMOF. For example, the reaction of alkenes **14a-c** with TTN in TMOF provided the resulting acetal products (**15a-c**) in 88%, 74%, and 79% yields, respectively (**Table 2**, entries 1-3) in contrast to the yields when HTIB was employed (29%, 28% and 34% yields, respectively) as depicted in **Table 1**, entries 1-3. The reaction of tosyl-protected alkenes **14d** with TTN in TMOF produced the resulting acetal **15d**, in 69% yield, with the *cis*-addition product **16d**, in 8% yield, and the *trans*-addition product **17d**, in 11% yield (**Table 2**, entry 4). Similarly, 2,4,6-trimethylbenzoyl-protected alkene **14e** gave the ring contraction product **15e** in 61% yield with two minor addition products *cis*- and *trans*-products, in 9% and 12% yields, respectively (**Table 2**, entry 5).

Table 2 TTN-mediated ring contraction reactions in TMOF.

Entry	Substrate	Acetal (Indane)	Addition product (*cis*)	Addition products (*trans*)
1	 **14a**	 **15a** 88%)		
2	 **14b**	 **15b** (74%)	***	***
3	 **14c**	 **15c** (79%)	***	***

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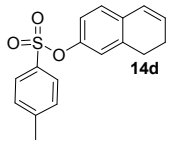
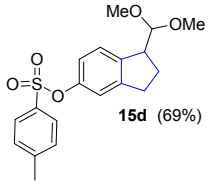
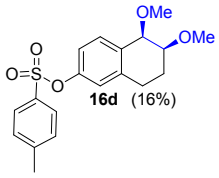
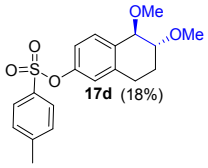
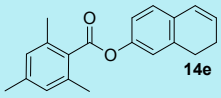
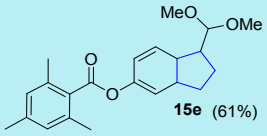
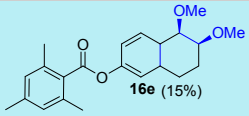
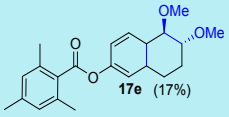
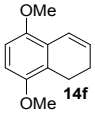
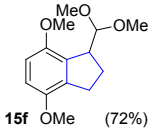
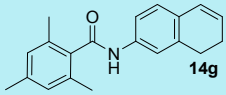
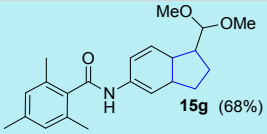
4	 **14d**	 **15d** (69%)	 **16d** (16%)	 **17d** (18%)
5	 **14e**	 **15e** (61%)	 **16e** (15%)	 **17e** (17%)
6	 **14f**	 **15f** (72%)	***	***
7	 **14g**	 **15g** (68%)	***	***

*** = *Compounds analyzed by TLC but could not characterized due to their low yields.*
***Reaction conditions**: 1.2 equiv TTN.3H$_2$O, TMOF, rt, 5 min*

Alkenes **14f** and **14g** were subjected to the TTN-mediated rearrangement reaction and the anticipated ring contraction products **15f** and **15g** were isolated in 72% and 68% yields, respectively (**Table 2**, entries 6 and 7). Comparing these yields with those reported in **Table 1** for the HTIB-mediated reactions, it is clear that TTN provides much better yields than HTIB. Additionally, a comparison of the yields reported in **tables 1** and **2** demonstrates that fewer addition or aromatization byproducts were observed when TTN was employed as the oxidizing agent. In conclusion, the reactions of the 1,2-dihydronaphthalenes with TTN proceeded in an efficient manner and provided good yields of the ring-contracted acetals.

The mechanism for the formation of indane via ring contraction reaction promoted by iodine(III) is described below in **Scheme 2**. This mechanism has also been recently investigated by the DFT (Density Functional Theory) calculation methods of computational chemistry.[49] The first step of the mechanism is the ionization of iodine(III), which leads to the formation of PhIOH$^+$, followed by its electrophilic addition to the double bond of alkene **13** to form the benzylic carbocation **14**. In the nucleophilic addition of the solvent, the theoretical approach of Solvation Model Density (SMD) continuum solvation model showed that the addition occurs via a cluster of solvent molecules. Moreover, DFT calculation also showed that the *trans*-addition of MeOH cluster to carbocation **14** occurs with less potential energy and less free energy as compared to their *cis* addition. The final step of the mechanism is the migration of the aryl group where the protonation of the hydroxyl group by the MeOH cluster **16**, followed by the elimination of H_2O, to

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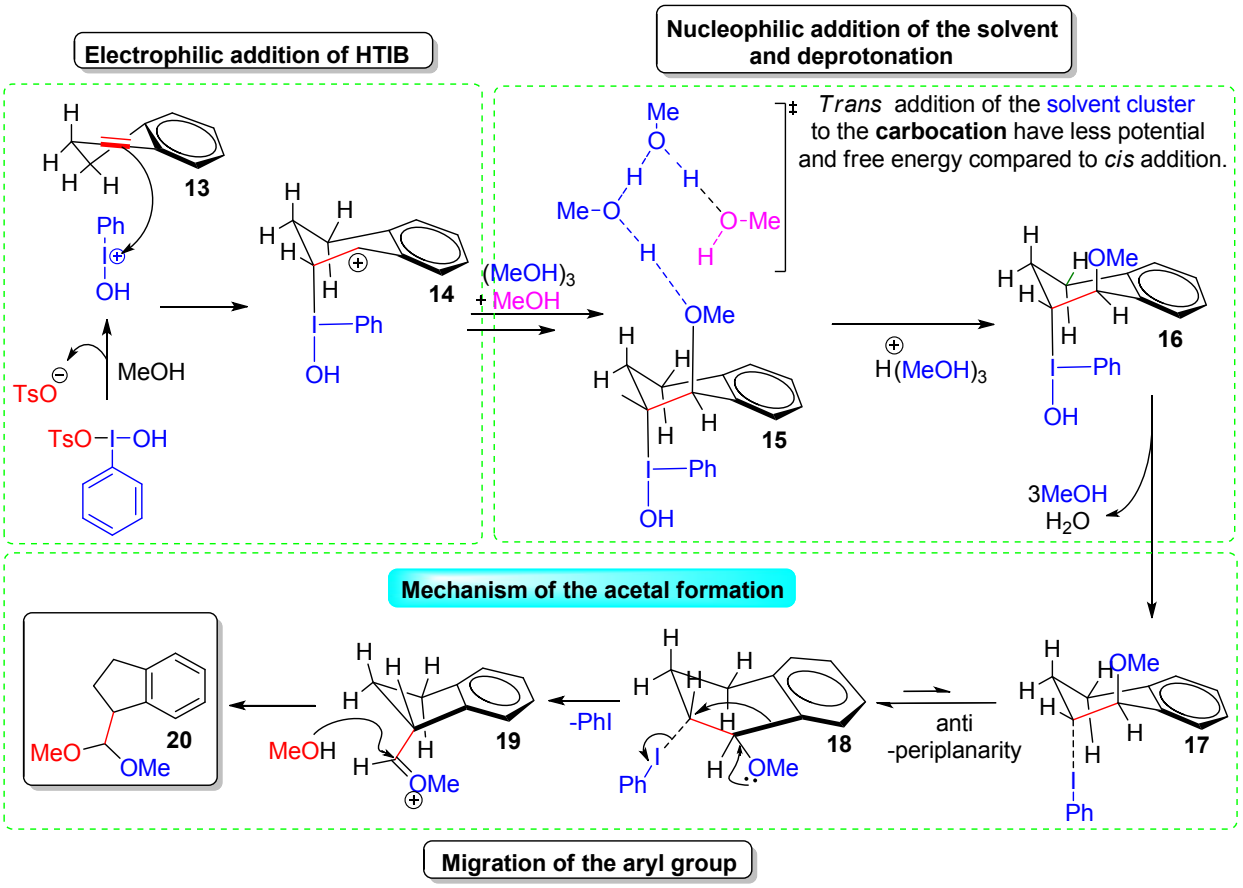
afford **17**. The C-I bond becomes weaker after the removal of H_2O and the required antiperiplanar **18** arrangement is formed. In the subsequent step, the formation of C-C bond followed by the loss of iodobenzene, ring contraction leads to a five-membered ring **20**.



Scheme 2 Ring contraction mechanism, mediated by iodine(III).

Scheme 3 summarizing the proposed mechanistic approaches, for the for the formation of *trans*- and *cis*-addition products.

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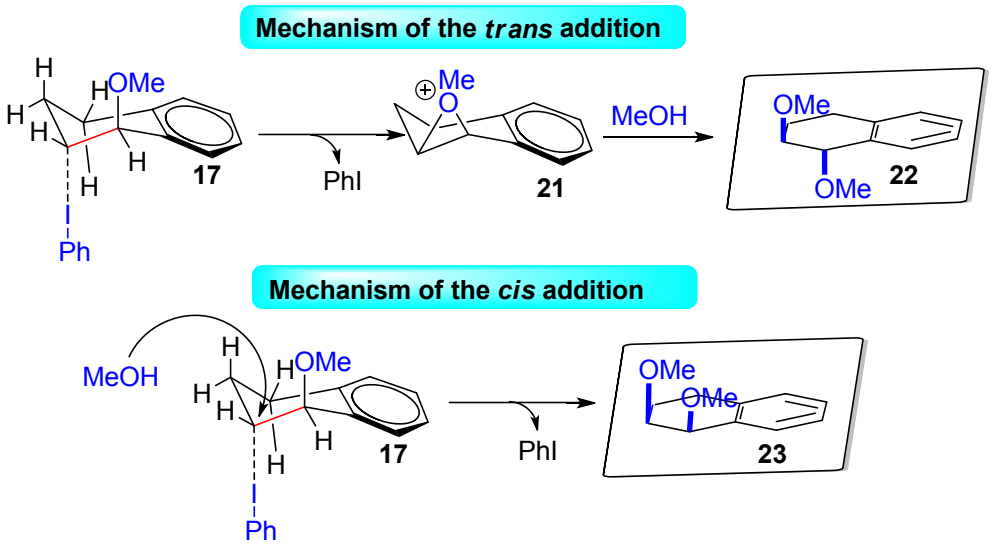

Scheme 3 HTIB-mediated mechanism for the formation of *trans*- and *cis*-addition products.

In the proposed mechanism,[28,31,50] the formation of the thallonium ion **24** is the first step. After the ring-opening occurs in a Markovnikov sense, the thallonium ion leads to the corresponding *trans* oxythallated adduct **25**. This intermediate subsequently undergoes rearrangement, giving the resulting acetal compound **20**, after the addition of MeOH to the oxonium **26**, and subsequent deprotonation (**Scheme 4A**).

In the case of *cis* and trans addition products, the thallonium ion **24** allowed ring-opening, which led to *trans* oxythallated adduct **25**, and the oxonium ion **27** is formed via the reductive elimination of thallium(III). The addition of a second solvent molecule leads to the *trans*-1,2-dimethoxylated isomer **22**, followed by deprotonation step (**Scheme 4C**). The formation of the *cis* isomer **23** would proceed directly from **25** after the elimination of the thallium(III) by the MeOH, followed by deprotonation step (**Scheme 4B**).

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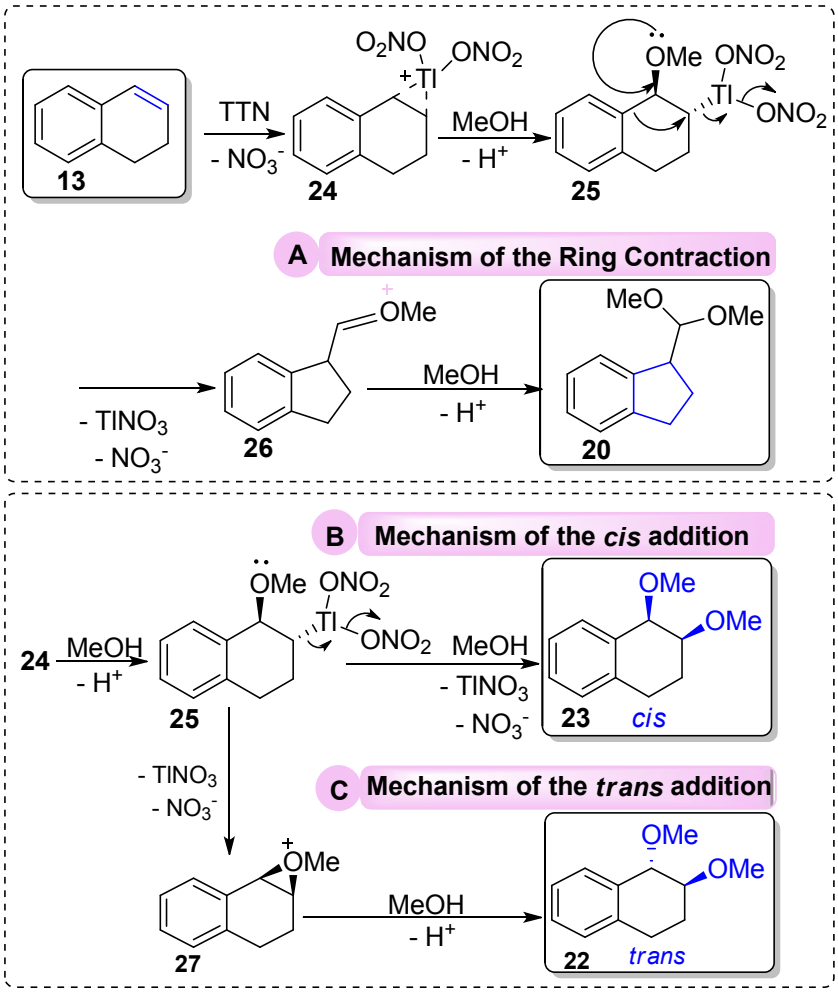

Scheme 4. Proposed mechanism for **A)** TTN-mediated ring contraction reaction; **B**) TTN-mediated *cis* dimethoxylated addition reaction; and **C**) TTN-mediated reactions for the *trans* dimethoxylated addition product.

Conclusion.

A series of protected 1,2-dihydronaphthalenes were subjected to HTIB and TTN in TMOF. Comparing these values of TTN-mediated reaction with those reported with HTIB-mediated, it is clear that the thallium(III) salt is much better than iodine(III) oxidizing agent for indane synthesis. Similarly, the TTN-mediated reactions are less prone to form addition byproducts compared to the HTIB-mediated reactions of 1,2-dihydronaphthalenes. Moreover, the tolerance of various protecting groups were also investigated while used thallium(III) and iodine(III). These findings will positively impact research towards indane synthesis for biomedical research.

Experimental.

HTIB-mediated oxidation of cyclic alkenes in TMOF; General procedure

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To the stirred solution of alkene **14b**-**14g** in TMOF (4 mL) was added 1.2 equiv HTIB at rt. After 5 min the reaction mixture was quenched by adding saturated solution of $NaHCO_3$ (10 mL), followed by extraction with DCM (3 x 10 mL), dried over anhydrous $MgSO_4$, filtrated and evaporated the solvents under vacume pressure. The crude residue was purified by flash column chromatography. (see characterization data for all novel compounds in ESI).

TTN.3H_2O-mediated oxidation of cyclic alkenes in TMOF; general reaction.

TTN.3H_2O (1.2 equiv) was added to the solution of alkenes **14a-g** in TMOF (4 mL) at rt and stirred for 5 min. The resulting precipitation was filtrated via silica gel pad (200-400 Mesh, *ca*, 10 cm), using CH_2Cl_2 as eluent. The filtrate was collected in conical flask was latter washed with H_2O (2 x 10 mL) and brain (10 mL) followed by drying over $MgSO_4$. Rota-evaporator was used to remove the solvent. The obtained crude residues were purified by flash column chromatography. Their Yields are given in the table 2, while physical states, IR (film), ^{1}H NMR and ^{13}C NMR data are given above.

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Conflicts of interest

There are no conflicts to declare

Author Contributions

A.K. Conceived the original synthetic proposal, carried out all the experimental work; M.R. and A.K. wrote the manuscript; and L.F.S. conceived the main idea.

Notes

Luiz F. Silva Jr.† In memoriam.

Supporting Information

Analytical data (^{1}H NMR, ^{13}C NMR) for all new compounds. see SI **DOI:**

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Table of contents entry

Ring contraction reactions were carried out using HTIB and TTN to compare yields as will as the protection group tolerance