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Tandem InCl_3 -promoted hydroperoxide rearrangements and nucleophilic additions, a straightforward entry to benzoxacycles

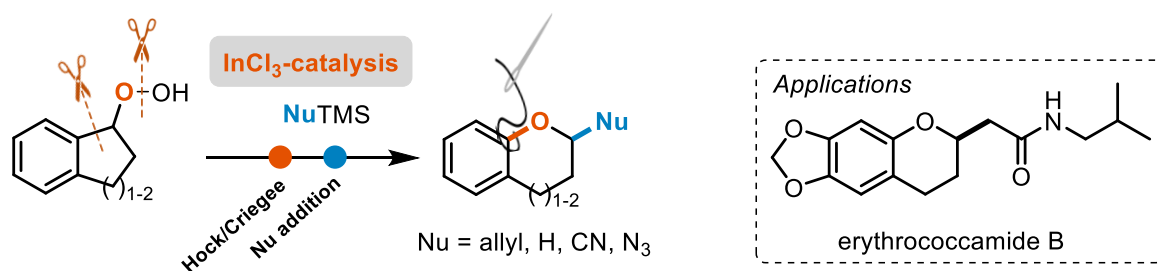
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Keywords: Hydroperoxide; Rearrangement; Benzoxacycles; Indium(III) catalysis; Tandem reactions

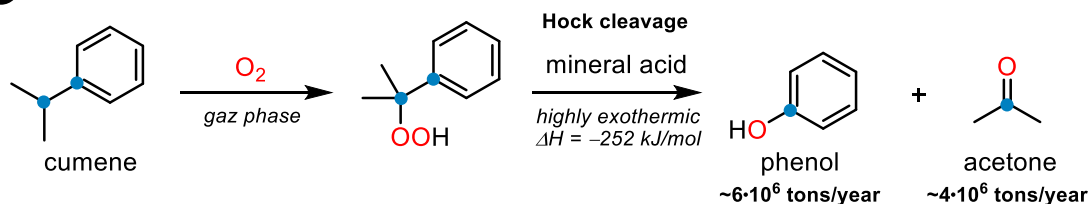


ABSTRACT: The acid-catalyzed rearrangement of organic peroxides is generally associated to C-C bond cleavages (Hock and Criegee rearrangements), with the concomitant formation of an oxocarbenium intermediate. This article describes the tandem process between a Hock or Criegee oxidative cleavage and a nucleophilic addition onto the oxocarbenium species (in particular a Hosomi-Sakurai-type allylation), under InCl_3 catalysis. It was applied to the synthesis of 2-substituted benzoxacycles (chromanes, benzoxepanes), including a synthesis of the 2-(aminomethyl)chromane part of sarizotan, and a total synthesis of erythrococcamide B.

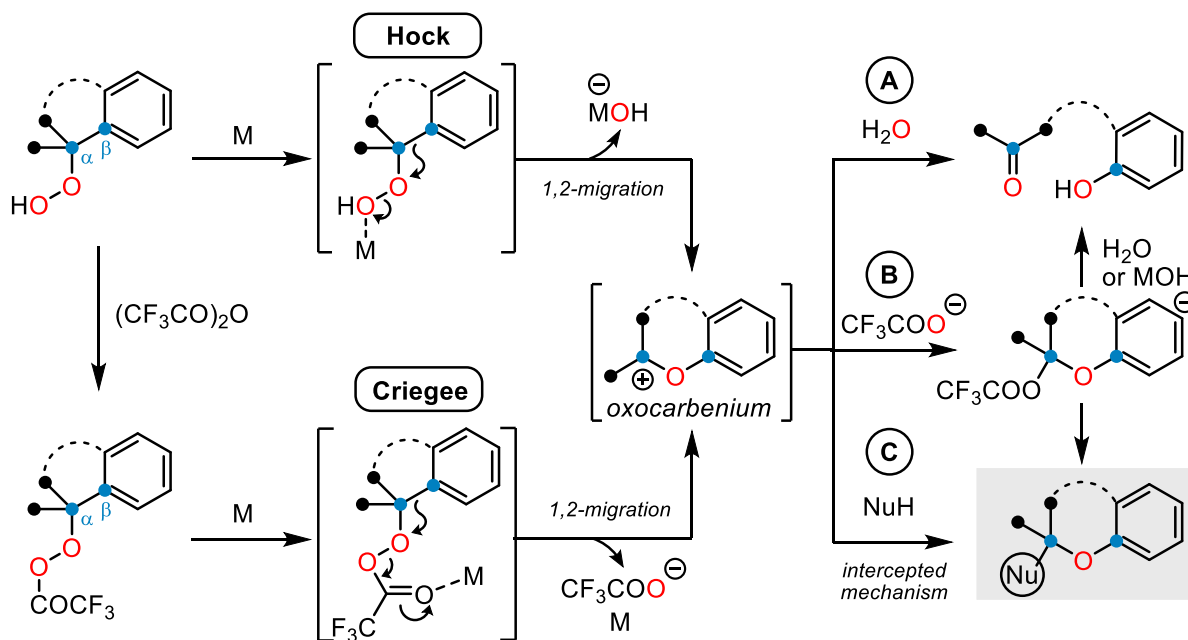
INTRODUCTION

The oxidative cleavage of organic hydroperoxides (Hock rearrangement¹) and related peresters (Criegee rearrangement²) constitutes a straightforward route to carbonyl and phenol derivatives.³ Important applications of the Hock cleavage concern the industrial cumene process, which allows the synthesis of millions tons of phenol and acetone each year (Scheme 1a),^{4,5} and the synthesis of artemisinin, a major antimalarial compound.⁶ It was also used to transform complex terpenoids, like cholesterol⁷ or diterpenic acids,⁸ in a bio-inspired manner. The Hock rearrangement involves a Brønsted or a Lewis acid catalysis that triggers the heterolytic cleavage of the C_α-C_β bond adjacent to the peroxide function, with concomitant 1,2-migration of the β carbon onto the nearest peroxide oxygen (Scheme 1b).^{3,9,10} Alternatively, the Criegee rearrangement relies on the activation of the hydroperoxide through a perester formation, weakening the O-O bond. These mechanisms are related to that of the Baeyer-Villiger rearrangement.¹¹⁻¹⁴ The peroxide cleavage is expected to form a transient oxocarbenium species, which is usually hydrolyzed (route A) into two carbonyl derivatives (or phenols), possibly through an acylal species that can be hydrolyzed in the Criegee mechanism¹⁵ (route B).

a The Hock (cumene) process



b Mechanism of peroxide rearrangements, rationalizing possible interruption with a nucleophile (M = H⁺ or Lewis acid)



Scheme 1. Hock and Criegee oxidative cleavages: (a) The cumene process; (b) Mechanism rationalizing a possible oxocarbenium interception by a nucleophile.

Recently, we investigated the mechanism of the InCl_3 -catalyzed Hock rearrangement through theoretical chemistry, detailing the formation of the oxocarbenium intermediate through a Wheland intermediate.¹⁶ Considering the electrophilicity of hypothetical oxocarbenium intermediates, the Hock and Criegee rearrangements can be considered as potential candidates to design interrupted versions by tandem additions of various nucleophiles^{17–20} (route C).

Brønsted or Lewis acids (*e.g.* TFA, TfOH, $\text{BF}_3 \cdot \text{OEt}_2$, AlCl_3 , SnCl_4 and more occasionally lanthanide triflates) have been used to catalyze the Hock cleavage.³ The industrial production of phenol mainly used mineral acids (*e.g.* H_2SO_4) and zeolites.^{4,5} However, there have been scarce systematic report on catalyst screening and applications.^{3,9,21} Interestingly, the selectivity of the Hock and Criegee rearrangements is strongly influenced by strain relief²² and by the electronic properties of substituents.^{10,23–25} The use of tandem and interrupted Hock reactions in the development of synthetic methodologies has been limited to few examples of allylation,⁹ oxindole rearrangements,^{26–28} an intramolecular Paal-Knorr synthesis of furans^{29,30} or a synthesis of carbazoles.³¹ The main drawback of such tandem reactions could be the critical competition with the hydrolysis resulting from the addition of a hydroxide residue (H_2O or MOH^- released during the hydroperoxide cleavage) onto the oxocarbenium intermediate. The Criegee rearrangement, which avoids the release of water, could provide a flexible solution to this problem.^{15,32} Herein, to develop these hypotheses, easily accessible indane and tetralin hydroperoxide substrates were used to afford the respective chromane and 1-benzoxepane products upon acid catalyzed rearrangements with a large scope of substituents.³³ The reactive oxocarbenium species formed in situ were expected to react with a series of nucleophiles to install substituents (allyl, cyano, azido or hydrogen upon reduction). This strategy was finally applied to the synthesis of valuable compounds, especially the natural product erythrocoamide B³⁴ and the 2-(aminomethyl)chromane part of sarizotan, an experimental drug tested to treat the breathing problems of the Rett syndrome (Figure 1).^{35,36}

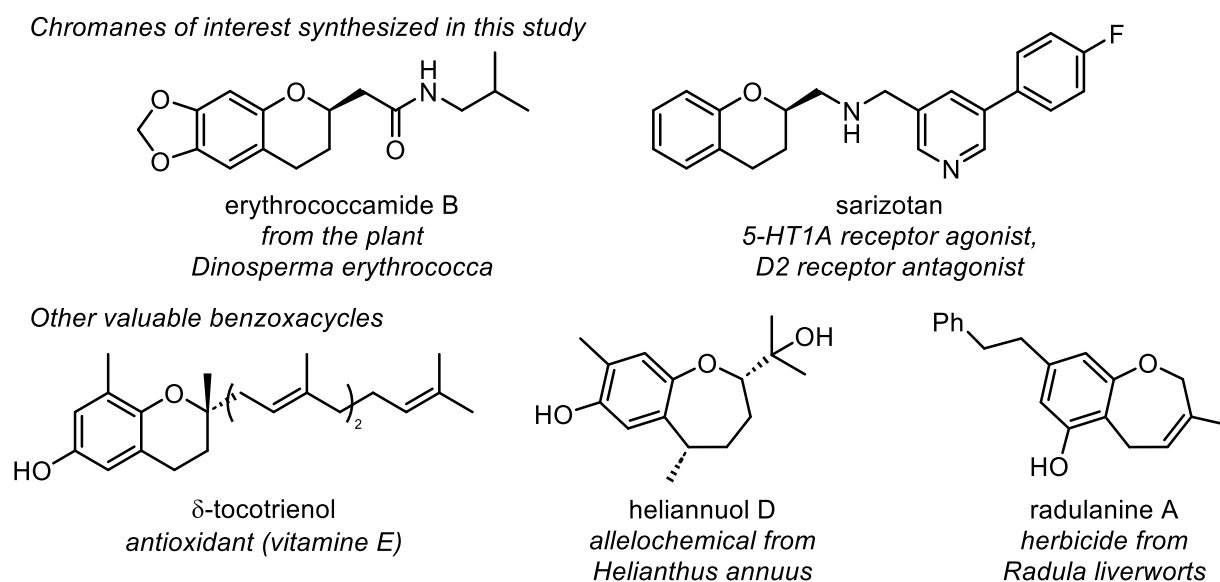
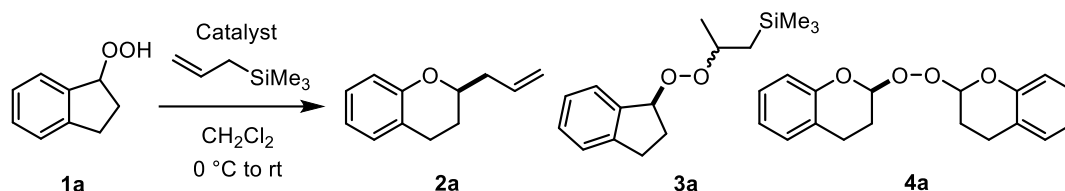


Figure 1. Examples of biologically significant benzoxacycles.

RESULTS AND DISCUSSION

The tandem Hock rearrangement–Hosomi-Sakurai allylation³⁷ was first investigated with indanyl hydroperoxide **1a** in presence of an acid catalyst and allyltrimethylsilane, to furnish 2-allylchromane **2a** (Table 1) [*Note that although the following organic peroxides were stable in our hands, it must be reminded that the manipulation of such reactive species must always be undertaken with great care*³⁸]. Decomposition was observed in the presence of BF₃·OEt₂ (2 equiv) at 0 °C (entry 1), while lowering the temperature at –78 °C afforded alkyl peroxide **3a** with no sign of Hock rearrangement (entry 2). The use of catalytic amounts of BF₃·OEt₂ (0.1 equiv) was inefficient (no reaction, entry 3). Although the Hock rearrangement was observed with pTsOH (entry 4) or TMSOTf³⁹ (entry 5), only bis(peroxyacetal) **4a** was identified (see reference 16 for a discussion of the structure determination), demonstrating the elimination and recombination of peroxide species during these reaction, while no reaction occurred with catalytic amounts of (PhO)₂PO₂H (entry 6). Catalytic amounts of Sn(OTf)₂, In(OTf)₃, Sc(OTf)₃ and AlCl₃ mostly led to complex mixtures of products (entries 7-10), but traces amounts of **2a** (3%) could be detected with In(OTf)₃. Copper(II) salts (entries 11 and 12) were able to promote the Hock cleavage, mainly resulting in peroxyacetal **4a**, while only Cu(ClO₄)₂ provided allylation product **2a**. To complete this catalyst screening, we were pleased to observe significant amounts of **2a** in presence of FeCl₃ and indium halides (entries 13-16), the most efficient catalyst being InCl₃ (0.1 equiv) with 62% of 2-allylchromane **2a**. Additional solvent screening showed that toluene (entry 17) and a coordinating solvent such as CH₃CN (entry 18) gave poor results compared to CH₂Cl₂. Overall, we observed that the Hock rearrangement can be promoted by most of the catalysts, especially InCl₃ and with the exception of BF₃·OEt₂, but only a few of them were able to perform the tandem Hosomi-Sakurai reaction (FeCl₃, Cu(ClO₄)₂ and In³⁺ salts in non coordinating solvent). Furthermore InCl₃ had previously been described by Baba and co-workers to be unable to perform the Hosomi-Sakurai allylation of aldehydes, unless a co-catalyst was added (TMSCl).⁴⁰ Interestingly, InCl₃ was recently used by Ferrié and co-workers to promote the Hosomi-Sakurai allylation of 1,2-dioxolan-3-yl acetates without affecting the endoperoxide group.⁴¹

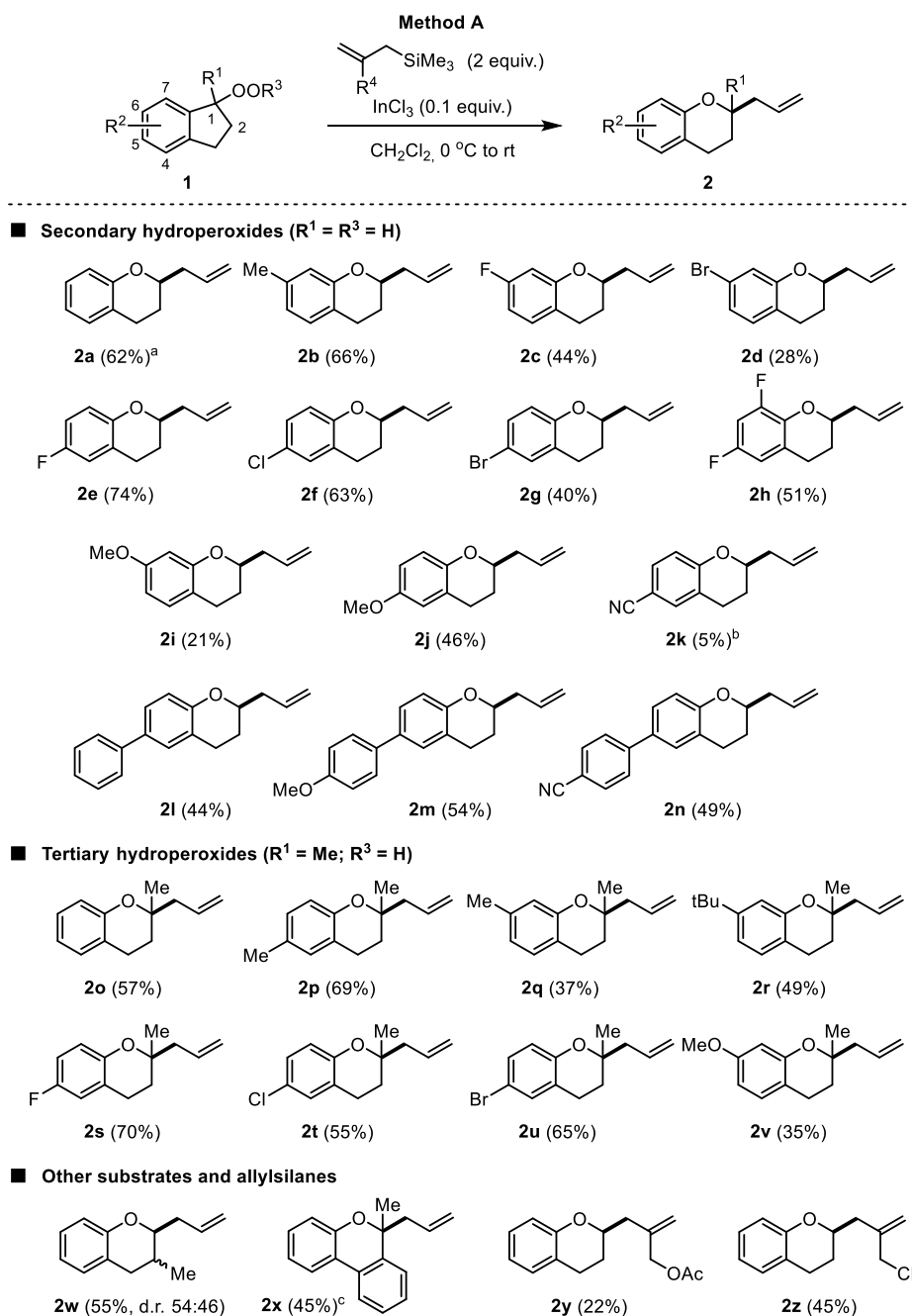
Table 1. Optimization of the tandem Hock/Hosomi-Sakurai reaction towards 2-allylchromane (**2a**).

| Entry | Catalyst or reagent (equiv), other remark | Ratio 1a:2a:3a:4a (yield of 2a , %) ^a |
|-----------|---|--|
| 1 | BF ₃ ·OEt ₂ (2) | Complex mixture |
| 2 | BF ₃ ·OEt ₂ (2), starting at -78 °C | 0:0:100:0 (0) |
| 3 | BF ₃ ·OEt ₂ (0.1) | -. ^b |
| 4 | pTsOH (0.1) | 0:0:0:100 (0) |
| 5 | TMSOTf (2) | 0:0:0:100 (0) |
| 6 | (PhO) ₂ PO ₂ H (0.1) | -. ^b |
| 7 | Sn(OTf) ₂ (0.1) | 15:0:70:15 (0) |
| 8 | In(OTf) ₃ (0.1) | 0:7:81:12 (3) |
| 9 | Sc(OTf) ₃ (0.1) | Complex mixture |
| 10 | AlCl ₃ (0.1) | Complex mixture |
| 11 | Cu(OTf) ₂ (0.1) | 0:0:30:70 (0) |
| 12 | Cu(ClO ₄) ₂ (0.1) | 0:35:0:65 (22) |
| 13 | FeCl ₃ (0.1) | 0:100:0:0 (30) |
| 14 | InBr ₃ (0.1) | 0:70:0:30 (22) |
| 15 | InI ₃ (0.1) | 0:100:0:0 (40) |
| 16 | InCl₃ (0.1) | 0:100:0:0 (62) |
| 17 | InCl ₃ (0.1) in PhMe | 55:45:0:0 (n.d.) ^c |
| 18 | InCl ₃ (0.1) in CH ₃ CN | 0:0:50:50 (n.d.) |

^a Ratio based on NMR integrations, and NMR yield relatively to internal standard 1,2-dichloroethane. ^b Mostly no reaction, with traces (<5%) of **2a**, **4a**, and decomposition products. ^c Not determined.

The best condition (0.1 equiv of InCl₃, 2 equiv of allyltrimethylsilane, CH₂Cl₂, 0 °C to room temperature, hereafter Method A) was applied to various 1-indanyl hydroperoxides (Scheme 2), including tertiary hydroperoxides, all synthesized from the corresponding indanones through a two-step sequence of reduction or Grignard addition⁴² on the ketone, and acid-catalyzed hydroperoxidation (see supporting information). With secondary hydroperoxides **1a-1n** (R¹ = R³ = H), the reaction was successful with various substituents on the aromatic ring. π -Donors in position 5 are favorable, especially halides. The presence of a strong π -donor like OMe led to higher reactivity, leading us to avoid any isolation of **1j** since the Hock reaction was partially observed during the

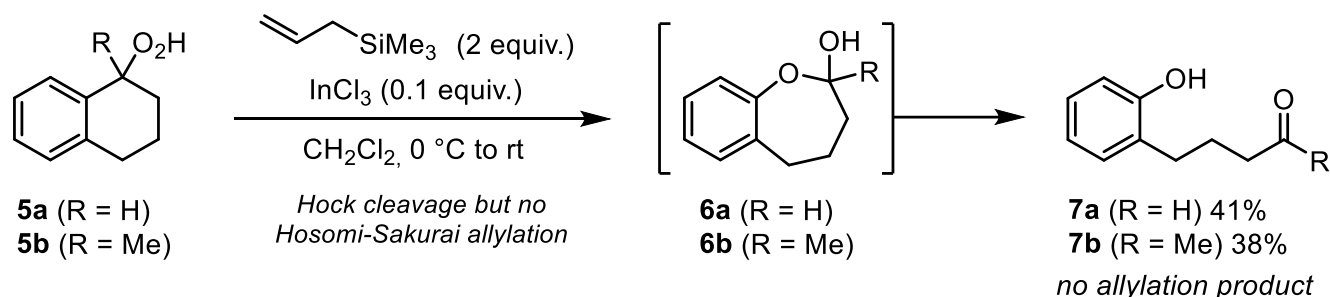
hydroperoxidation step. Thus, performing the allylation on a crude hydroperoxide extract of **1j** led to product **2j** in 46% yield. On the contrary, a strong π -acceptor like a CN group was detrimental to the tandem reaction, leading to **2k** with a low yield only (5%). In that case, a lactol side product (compound **S2** in the Supporting Information) was nevertheless isolated in 21% yield along with 22% of recovered starting material, showing the low performance of the Hock reaction on electron-deficient substrates like **1k**. Biphenyl derivatives (**1l-1n**) were tested with different *para*-substituents, showing a similar reactivity trend in presence of a OMe (54% of **2m**) or a CN (49% of **2n**) resulting from a "shielding" effect of the phenyl ring towards the substituent electronic properties.



Scheme 2. Tandem Hock/Hosomi-Sakurai reactions of 1-indanyl hydroperoxides through method A. ^a The *tert*-butyl peroxide of **1** gave a similar yield of 64%. ^b Lactol side product **S2** was also isolated in 21% yield, along with 22% of starting material **1k** (see the Supporting Information). ^c From *tert*-butyl peroxide **1x** (R³ = *t*-Bu).

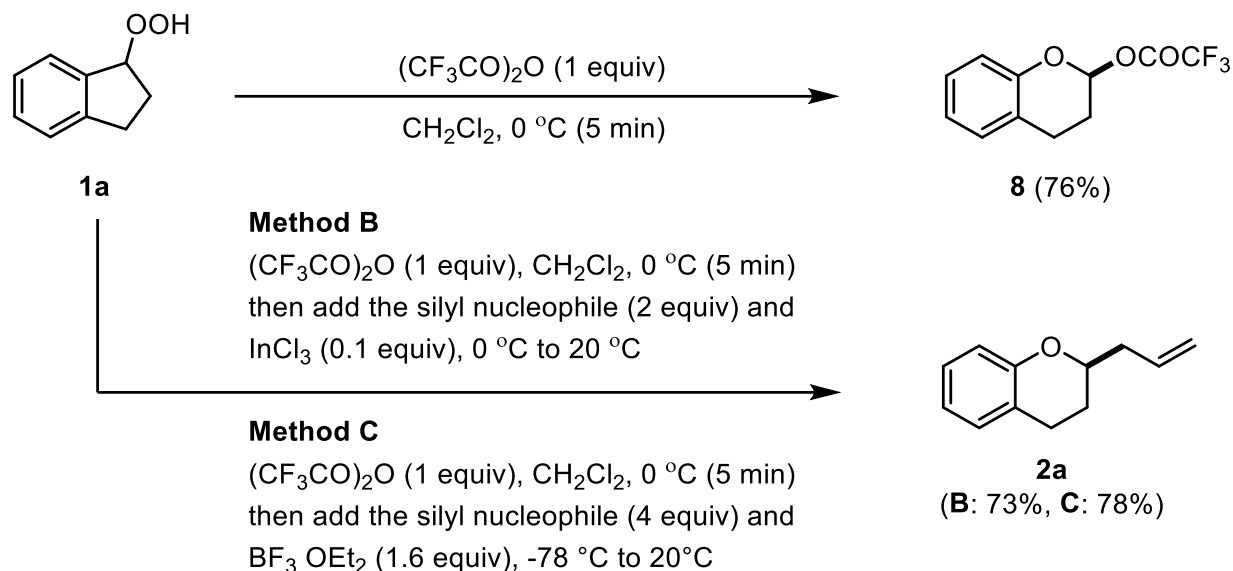
Furthermore, we observed that tertiary hydroperoxides **1o-1v** ($R^1 = \text{Me}$; $R^3 = \text{H}$) performed well to provide the allylation products. The presence of a methyl substituent in position 2 of the indane core (**1w**) led to a diastereomeric mixture (55% yield) with a 46:54 ratio in slight favor of *anti* compound **2w**. The tandem reaction was also applicable to tertiary fluorenyl *tert*-butyl peroxide **1x** ($R^3 = t\text{-Bu}$) to give tricyclic chromane **2x**. Finally, it was possible to perform the allylation with branched allylsilanes ($R^4 = \text{CH}_2\text{OAc}$ or CH_2Cl), though in lower yields, giving allyl acetate **2y** and chloride **2z** in only 22% and 45% yields. Incidentally, in the same conditions, the 1-indanyl *tert*-butyl peroxide of **1a** ($R^1 = R^2 = \text{H}$, $R^3 = t\text{-Bu}$) afforded chromane **2a** in 64% yield, showing a similar reactivity as the hydroperoxide substrate ($R^3 = \text{H}$).

Starting from 1-tetralinyl hydroperoxides **5a** and **5b** (Scheme 3), method A quantitatively gave typical Hock cleavage products (**7a** and **7b** in *ca.* 40%). These products result from the formal addition of a hydroxide group released during the Hock cleavage onto the oxocarbenium intermediates, followed by the rapid opening of the resulting seven-membered lactols **6a** and **6b** (Scheme 3). Unfortunately, we never observed any allylation under these conditions, leading us to investigate an alternative method.



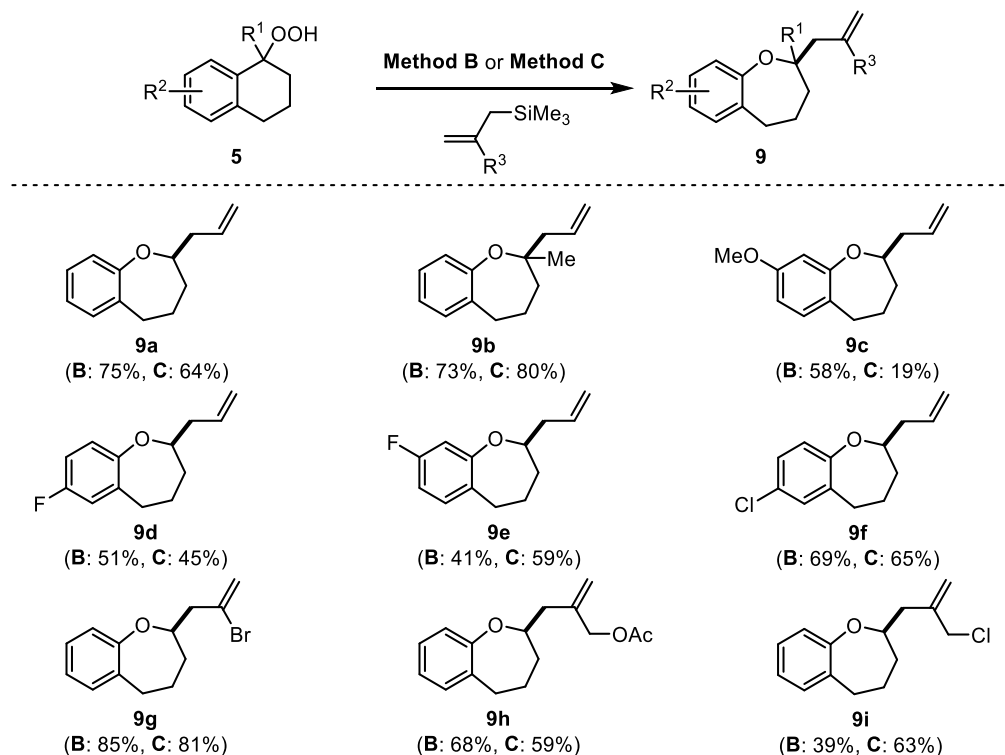
Scheme 3. Application of method A to 1-tetralinyl hydroperoxides, showing no tandem allylation.

To avoid the opening of lactol intermediates **6a/b**, we envisaged to apply the Criegee rearrangement in a tandem process with the Hosomi-Sakurai allylation. According to Kishi,¹⁵ the Criegee rearrangement can be performed in presence of a carboxylic anhydride to activate the hydroperoxide, releasing a carboxylate that can react back onto the oxocarbenium intermediate, thus affording a transient acylal product (see Scheme 1B). In presence of a nucleophile and an appropriate catalyst, this acylal could thus lead to the coupling product in a one-pot process. Testing the reaction on 1-indanyl hydroperoxide **1a** in presence of trifluoroacetic anhydride in CH_2Cl_2 and in the absence of nucleophile, it was possible to isolate *O*-trifluoroacetyl lactol **8** in 76% yield, in accordance with Kishi's report (Scheme 4).¹⁵ Under similar conditions, after completion of the Criegee rearrangement revealed by thin layer chromatography, the addition of allyltrimethylsilane to the reaction mixture did not afford the allylation product (**2a**), but a complex mixture. Compound **2a** was however cleanly obtained in 70-80% yields when a Lewis acid catalyst was added concomitantly with the nucleophile, here InCl_3 (0.1 equiv, Method B) or $\text{BF}_3 \cdot \text{OEt}_2$ (1.6 equiv, Method C).



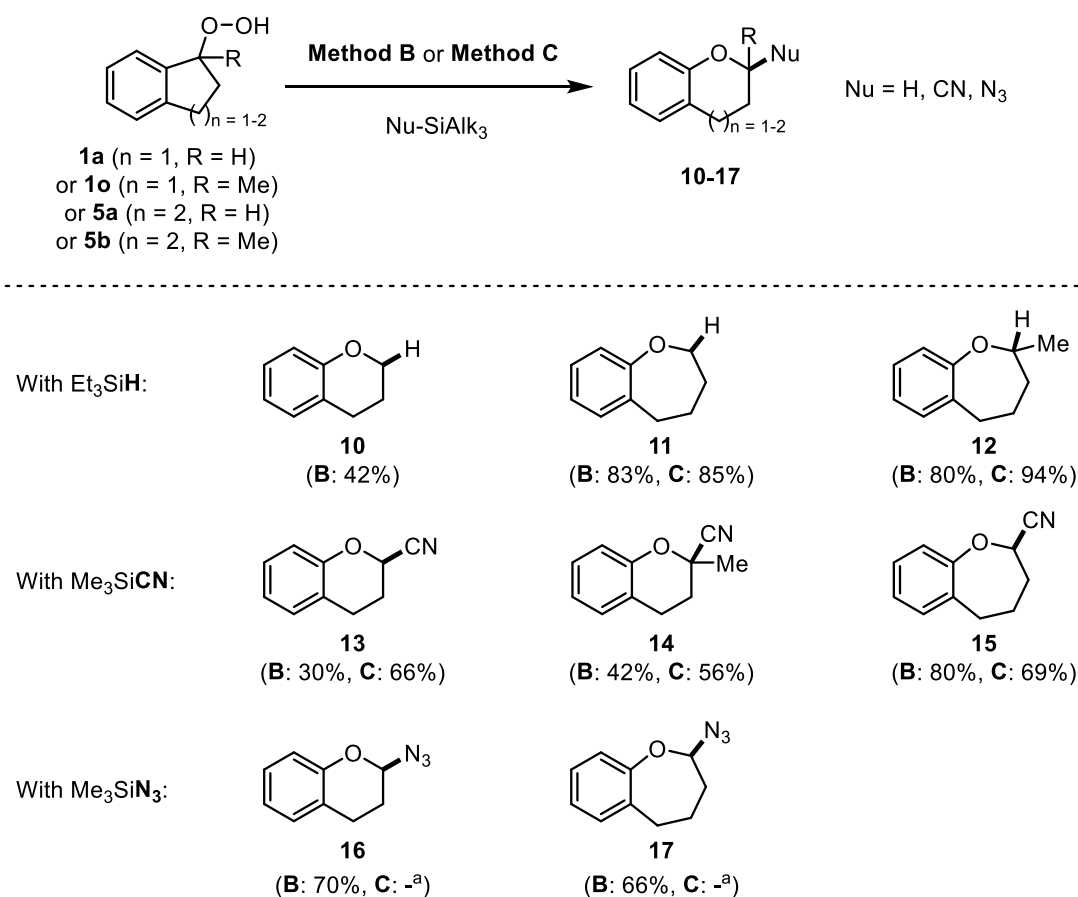
Scheme 4. Reactivity and allylation of 1-indanyl hydroperoxide under Criegee reaction conditions.

Methods B and C were applied to 1-tetralinyl hydroperoxide substrates (**5**, Scheme 5). The 2-allylbenzoxepane derivatives (**9a-9i**) could be obtained in moderate to good yields (50-80%) in all cases. Although method B is better than method C in terms of reagent economy and should be preferred for larger scale applications, method C offers some advantages to improve yields with a few substrates (**9e**, **9i**). Furthermore, the transformation was applicable to a tertiary hydroperoxide (giving **9b**), and to substituted or branched allyltrimethylsilanes (**9g-9i**).



Scheme 5. Application of the tandem Criegee/Hosomi-Sakurai reaction to the synthesis of benzoxepanes.

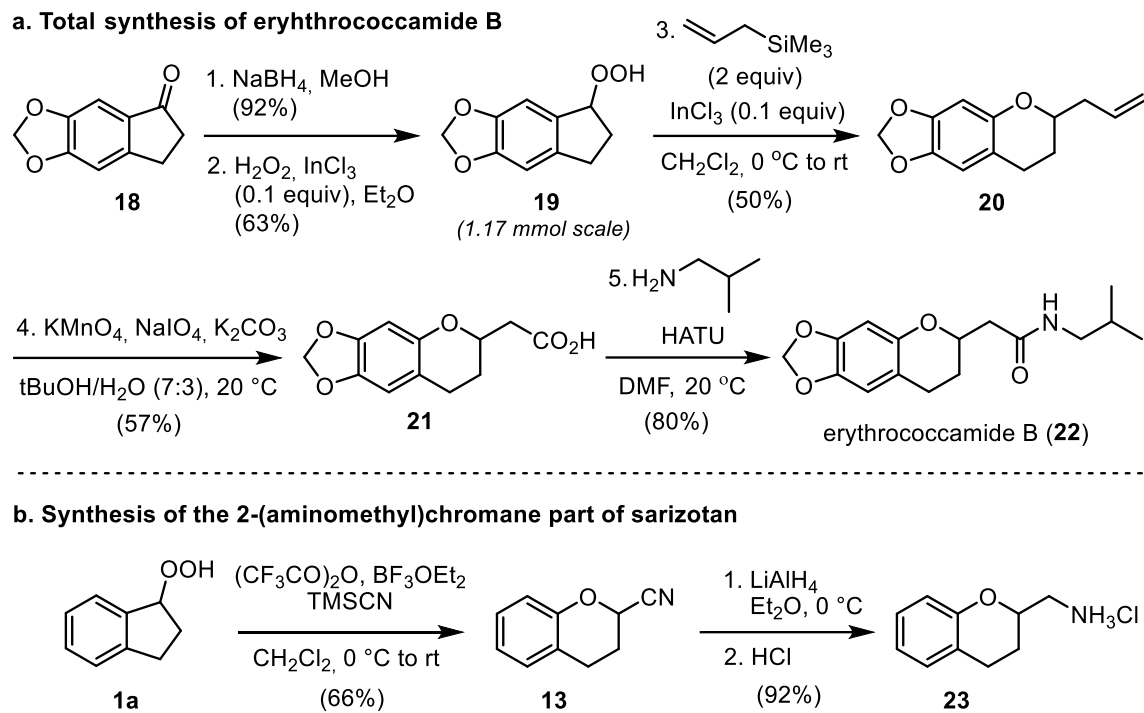
Finally, we transposed this one-pot sequence to the tandem addition of other nucleophilic partners¹⁷⁻²⁰ like Et₃SiH (hydride donor), Me₃SiCN (cyanide donor) and Me₃SiN₃ (azide donor), giving the corresponding chromane and benzoxepane products in generally good yields (Scheme 6). These additional nucleophiles were only applicable to methods B and C. Other nucleophiles like 1,3,5-trimethoxybenzene or indole derivatives were unfortunately unsuccessful, unlike other studies.^{26,27} Interestingly, differences could be observed between the two sets of conditions, suggesting their complementarity. In particular, the azidation sequence was only possible with InCl₃, giving satisfying yields *ca.* 70%, while BF₃·OEt₂ always led to decomposition, supposedly due to BF₃-promoted azide rearrangements.⁴³ Finally, it must be mentioned that the presence of the TMS group on all these nucleophiles is required for the success of the reaction.



Scheme 6. Tandem reactions with other nucleophilic silanes: Et₃SiH, Me₃SiCN, Me₃SiN₃. ^a Decomposition was observed.

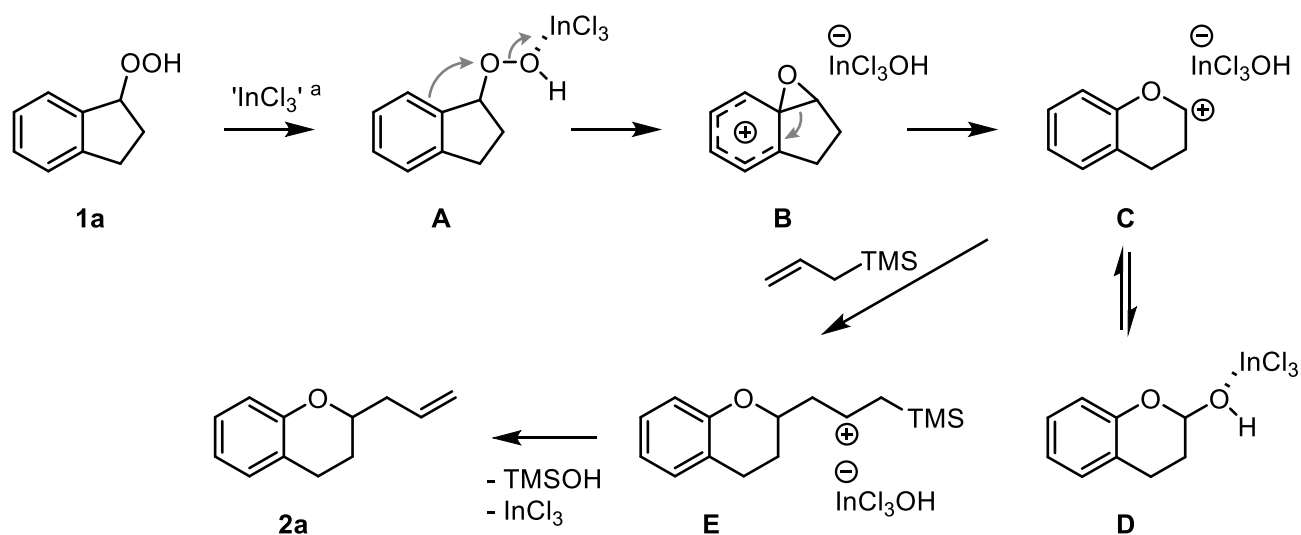
Benzoxacycles are important building blocks in natural products and are considered as privileged structures in medicinal chemistry (Figure 1).⁴⁴ The chromane scaffold is the lead-core of flavonoids, vitamins E, or of synthetic drugs like sarizotan.^{35,36} The benzoxepane core is also frequently found in biologically active natural products like heliannuols or radulanines.^{45,46} To demonstrate the interest of these tandem reactions, we applied method A to the total synthesis of erythrocoamide

B³⁴ (**22**, Scheme 7a), and method C to the synthesis of the 2-(aminomethyl)chromane moiety of sarizotan (**23**, Scheme 7b). The hydroperoxide **19**, made from indanone **18**, was submitted to the tandem Hock/Hosomi-Sakurai reaction using method A to give chromane **20** in 50% yields (1.17 mmol scale). The KMnO₄-mediated oxidative cleavage of the double bond to form carboxylic acid **21**, followed by the formation of the isobutyl amide, finally afforded natural product **22**. Concerning sarizotan chromane **23**, it was synthesized by the reduction of cyanide **13**, available from 1-indanyl hydroperoxide (**1a**) through the tandem Criegee rearrangement/cyanation protocol, following method C in presence of Me₃SiCN. Comparatively, the synthesis of **23** was previously achieved from chromane-2-carboxylates.⁴⁷⁻⁴⁹



Scheme 7. Synthetic applications of tandem oxidative cleavage/nucleophile addition.

From a mechanistic point of view regarding the InCl₃-promoted Hock rearrangement, this experimental study opens interesting questions on the influence of the substituents on the hydroperoxide rearrangement, the catalytic character of InCl₃ and the nature of the active metallic species, or the preferential migration of the sp² carbon compared to the sp³ carbon. These questions, of a more fundamental nature have been the subject of a theoretical investigation in a separate article.¹⁶ Based on this study and previous hypotheses concerning the Hosomi-Sakurai allylation,¹⁷ we propose a mechanism for the present tandem transformation (Scheme 8). The rearrangement would start with the O–O bond cleavage and the concomittant formation of a Wheland intermediate (**A** to **B**). The C–C bond cleavage of **B** would result in the rearomatisation and the formation of an electrophilic species (**C**) capable to react with the nucleophile, finally leading to the allylchromane product **2a** through **E**.



Scheme 8. Proposed mechanism of the InCl_3 -promoted Hock rearrangement¹⁶ and Hosomi-Sakurai allylation. ^aNote that InCl_3 is always coordinated and does not exist in a free monomeric form (see ref. 16 for details).

CONCLUSION

In conclusion, we developed a straightforward route to synthesize chromanes and benzoxepanes from indanyl or tetralinyl hydroperoxides, respectively. The general strategy was based on a tandem Hock or Criegee rearrangement coupled to nucleophilic additions, and was efficiently promoted by InCl_3 . In general, we demonstrated the superiority of InCl_3 over other Lewis acids in this transformation. Various nucleophiles, all being activated as trialkylsilanes, allowed the addition of allyl, hydride, cyanide or azide on the oxocarbenium species generated in situ. The method was successfully applied to the total synthesis of the natural product erythrocoamide B and the chromane core of the drug sarizotan. Owing to the important place of the Hock rearrangement in the chemical industry, and that of benzoxacycles in medicinal chemistry, we expect these results could have a significant impact in drug development and fine chemistry.

Supporting Information

Description of experimental procedures including copies of NMR spectra (PDF).

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