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

Alexandra E. Bosnidou,[1] Agathe Fayet,[1,2] Cristina Cheibas,[1] Oscar Gayraud,[1] Sophie Bourcier,[3] Gilles Frison*,[2] and Bastien Nay*,[1]

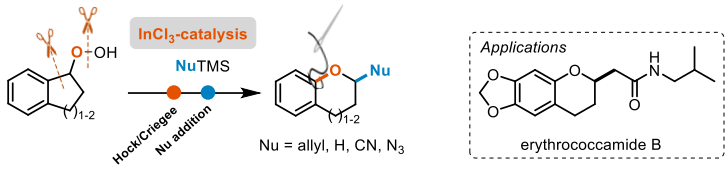
[1] Laboratoire de Synthèse Organique, Ecole Polytechnique, CNRS, ENSTA, Institut Polytechnique de Paris, Palaiseau, France

[2] Sorbonne Université, CNRS, Laboratoire de Chimie Théorique, 75005 Paris, France

[3] Laboratoire de Chimie Moléculaire, Ecole Polytechnique, CNRS, Institut Polytechnique de Paris, Palaiseau, France

Supporting Information Placeholder

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

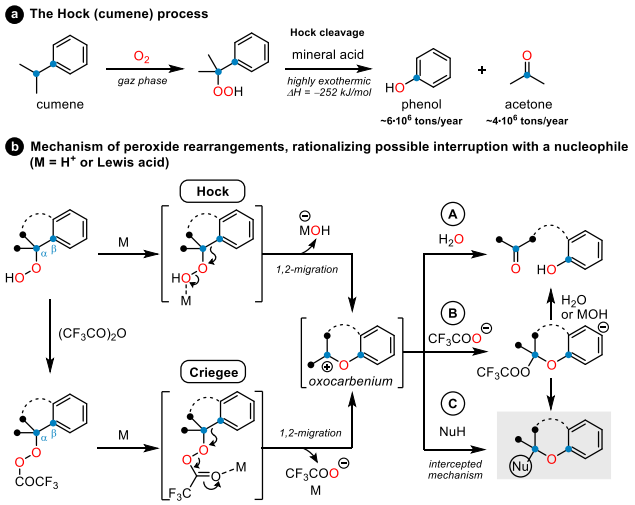


ABSTRACT: The acid-catalyzed rearrangement of organic peroxides is generally associated to C-C-bond cleavages (Hock and Criegee rearrangements), with the concommittent formation of an oxocarbenium intermediate. This article describes the tandem process between a Hock or Criegee oxidative cleavage and a nucleophilic addition onto the oxocarbenium species (in particular a Sakurai-Hosomi-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 rearrangement[1]) and related peresters (Criegee rearrangement[2]) 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 cholesterol[7] 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 mechanism[15] (route B).

Scheme 1. Hock and Criegee oxidative cleavages: (a) the cumene process and (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 oxocarbenium intermediates, the Hock and Criegee rearrangements can be considered as potential candidates to design interrupted versions by tandem nucleophilic additions (route C).

Brønsted or Lewis acids (*e.g.* TFA, TfOH, $BF_3{\cdot}OEt_2$, $AlCl_3$, $SnCl_4$ 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 zeolithes.[4,5] However, there have been scarce systematic studies on the catalyst scope and applications.[3,9,17] Interestingly, the selectivity of the Hock and Criegee rearrangements is strongly influenced by strain relief[18] and by the electronic properties of substituents.[10,19–21] The use of tandem and interrupted Hock reactions in the development of new synthetic methodologies has been limited to few examples of allylation,[9] an intramolecular Paal-Knorr synthesis of furans[22,23] or a synthesis of carbazoles.[24] 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.[15,25] 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. 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 erythrococcamide B[26] and the 2-(aminomethyl)chromane part of sarizotan, an experimental drug tested to treat the breathing problems of the Rett syndrome (Figure 1).[27,28]

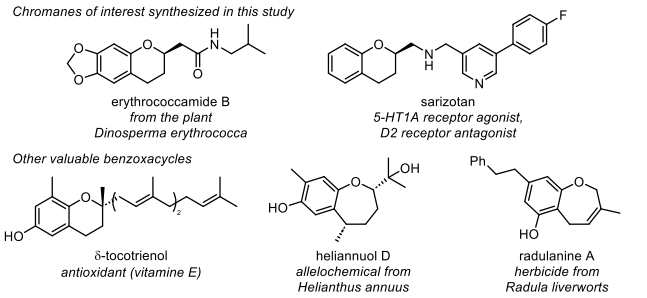
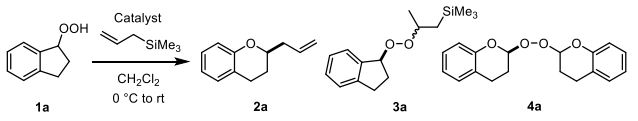


Figure 1. Examples of biologically significant benzoxacycles.

RESULTS AND DISCUSSION

The tandem Hock rearrangement–Sakurai-Hosomi allylation was first investigated with indanyl hydroperoxide **1a** in presence of an acid catalyst and allyltrimethylsilane, to furnish 2-allylchromane **2a** (Table 1). Decomposition was observed in the presence of $BF_3{\cdot}OEt_2$ (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 $BF_3{\cdot}OEt_2$ (0.1 equiv) was inefficient (no reaction, entry 3). Although the Hock rearrangement was observed with pTsOH (entry 4) or TMSOTf[29] (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 $(PhO)_2PO_2H$ (entry 6). Catalytic amounts of $Sn(OTf)_2$, $In(OTf)_3$, $Sc(OTf)_3$ and $AlCl_3$ 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 $Cu(ClO_4)_2$ provided allylation product **2a**. To complete this catalyst screening, we were pleased to observe significant amounts of **2a** in presence of $FeCl_3$ and indium halides (entries 13-16), the most efficient catalyst being $InCl_3$ (0.1 equiv) with 62% of 2-allylchromane **2a**. Additional solvent screening showed that toluene (entry 17) and a coordinating solvent such as CH_3CN (entry 18) gave poor results compared to CH_2Cl_2. Overall, we observed that the Hock rearrangement can be promoted by most of the catalysts, especially $InCl_3$ and with the exception of $BF_3{\cdot}OEt_2$, but only a few of them were able to perform the tandem Sakurai-Hosomi reaction ($FeCl_3$, $Cu(ClO_4)_2$ and In^{3+} salts in non coordinating solvent). Furthermore $InCl_3$ had previously been described by Baba and co-workers to be unable to perform the Sakurai-Hosomi allylation of aldehydes, unless a co-catalyst was added (TMSCl).[30] Interestingly, $InCl_3$ was recently used by Ferrié and co-workers to promote the Sakurai-Hosomi allylation of 1,2-dioxolan-3-yl acetates without affecting the endoperoxide group.[31]

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



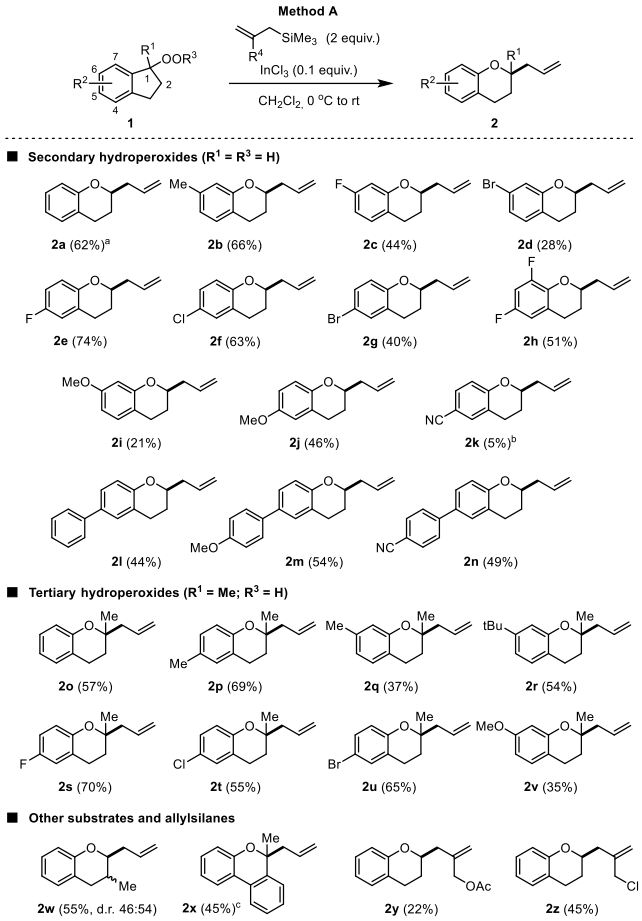
Entry	Catalyst or reagent (equiv), other remark	Ratio **1a**:**2a**:**3a**:**4a** (yield of **2a**, %)[a]
1	$BF_3{\cdot}OEt_2$ (2)	Complex mixture
2	$BF_3{\cdot}OEt_2$ (2), starting at –78 °C	0:0:100:0 (0)
3	$BF_3{\cdot}OEt_2$ (0.1)	-[b]
4	pTsOH (0.1)	0:0:0:100 (0)
5	TMSOTf (2)	0:0:0:100 (0)
6	$(PhO)_2PO_2H$ (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	**$InCl_3$ (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_3CN	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 $InCl_3$, 2 equiv of allyltrimethylsilane, CH_2Cl_2, 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 addition[32] on the ketone, and acid-catalyzed hydroperoxidation (see supporting information). With secondary hydroperoxides **1a-1n** (R^1 = R^3 = 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 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/Sakurai-Hosomi reactions of 1-indanyl hydroperoxides through method A.

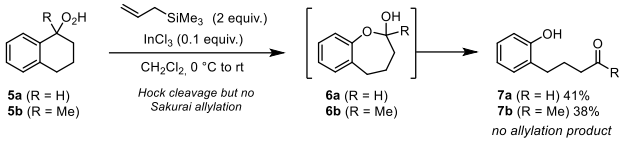


[a] The *tert*-butyl hydroperoxide of **1** gave a similar yield of 64%. [b] Lactol side product **S2** was also isolated in 21% yield, along with 22% of starting material **1k** (see the Supporting Information). [c] From *tert*-butyl hydroperoxide **1x** (R^3 = *t*-Bu).

Furthermore, we observed that tertiary hydroperoxides **1o-1v** (R^1 = Me; R^3 = 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 = tBu) to give tricyclic chromane **2x**. Finally, it was possible to perform the allylation with branched allylsilanes (R^4 = CH_2OAc 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 = H, R^3 = *t*-Bu) afforded chromane **2a** in 64% yield, showing a similar reactivity as the hydroperoxide substrate (R^3 = H).

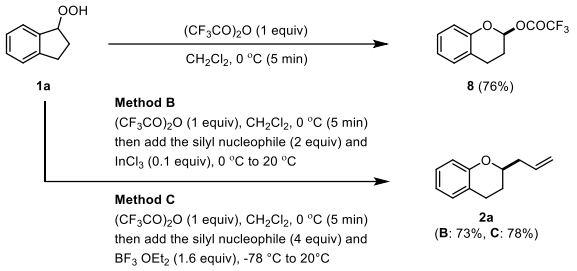
Starting from 1-tetralinyl hydroperoxides **5a** and **5b** (Scheme 3), method A quantitatively gave typical Hock cleavage products (**7a** and **7b** in *ca.* 40%). These products result from the formal addition of a hydroxide group released during the Hock cleavage onto the oxocarbenium intermediates, 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.



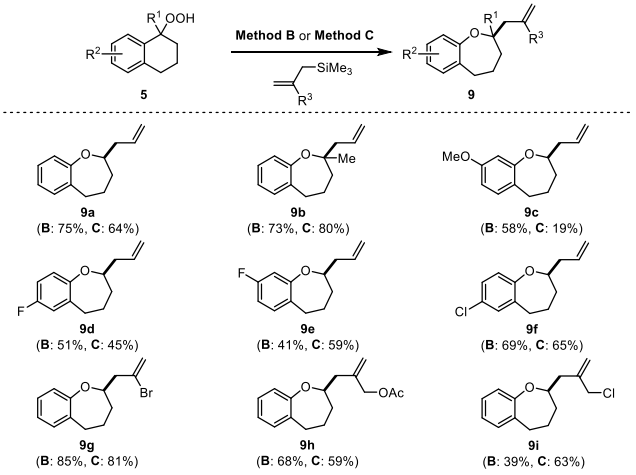
To avoid the opening of lactol intermediates **6a/b**, we envisaged to apply the Criegee rearrangement in a tandem process with the Sakurai-Hosomi allylation. According to Kishi,[15] the Criegee rearrangement can be performed in presence of a carboxylic anhydride to activate the hydroperoxide, releasing 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 concomitently with the nucleophile, here $InCl_3$ (0.1 equiv, Method B) or $BF_3{\cdot}OEt_2$ (1.6 equiv, Method C).

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



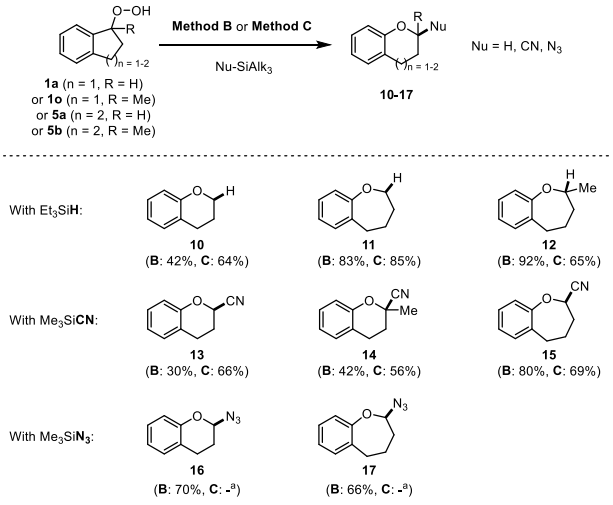
Methods B and C were applied to 1-tetralinyl hydroperoxide substrates (**5**, Scheme 5). The 2-allylbenzoxepane derivatives (**9a-9i**) could be obtained in moderate to good yields (50-80%) in all cases. Although method B is better than method C in terms of reagent economy and should be preferred for 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/Sakurai-Hosomi reaction to the synthesis of benzoxepanes.



Finally, we transposed this one-pot sequence to the tandem addition of other nucleophilic partners like Et_3SiH (hydride donor), Me_3SiCN (cyanide donor) and Me_3SiN_3 (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. Interestingly, differences were observed between the two sets of conditions (see for example product **13**), suggesting their complementarity. In particular, the azidation sequence was only possible with $InCl_3$, giving satisfying yields *ca.* 70%, while $BF_3{\cdot}OEt_2$ always led to decomposition, supposedly due to BF_3-promoted azide rearrangements.[33]

Scheme 6. Tandem reactions with other nucleophilic silanes: Et_3SiH, Me_3SiCN, Me_3SiN_3.

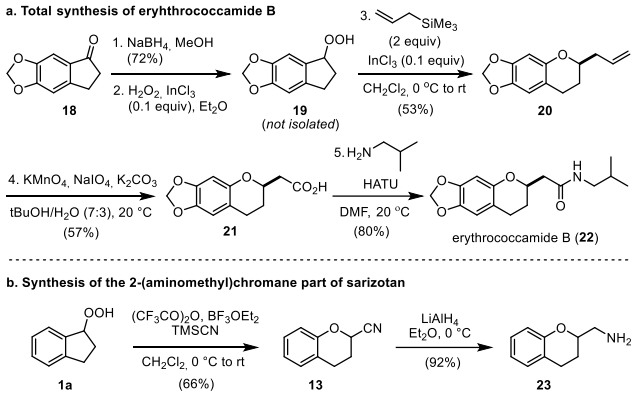


[a] Decomposition was observed.

Benzoxacycles are important building blocks in natural products and are often considered as privileged structures in medicinal chemistry (Figure 1).[34] The chromane scaffold is the lead-core of flavonoids, vitamins E, or of synthetic drugs like sarizotan.[27,28] The benzoxepane core is also frequently found in biologically active natural products like heliannuols or radulanines.[35,36] To demonstrate the interest of these tandem reactions, we applied method A to the total synthesis of erythrococcamide B[26] (**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/Sakurai-Hosomi reaction using method A to give chromane **20** in 53% yields. The $KMnO_4$-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 Me_3SiCN. Comparatively, the synthesis of **23** was previously achieved from chromane-2-carboxylates.[37–39]

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



From a mechanistic point of view, this experimental study opens several interesting questions, in particular on the influence of the substituents and their position on the hydroperoxide rearrangement, the catalytic character of the $InCl_3$-promoted reaction, the preferential migration of the sp^2 carbon compared to the sp^3 carbon, or the nature of the active metallic species when using $InCl_3$. These questions, of a more fundamental nature, are outside the scope of this experimental study, and are the subject of a separate article.[16]

CONCLUSION

In conclusion, we developped 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 erythrococcamide 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.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Description of experimental procedures (PDF), copies of NMR spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

* Emails: bastien.nay@polytechnique.edu and gilles.frison@cnrs.fr

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