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Synthesis of 3,5-Disubstituted 1,2-Dioxolanes through the Use of Acetoxy Peroxyacetals

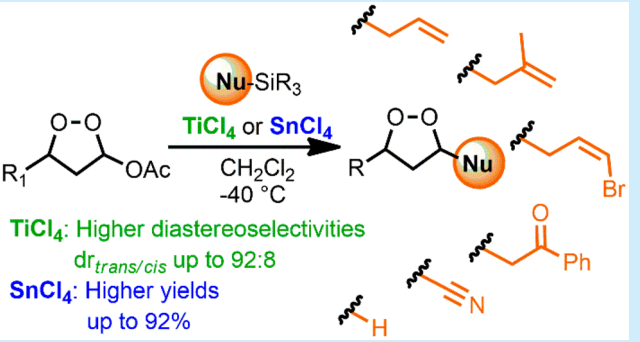
Alexis Pinet,[†] Thuy Linh Nguyen,[†,‡] Guillaume Bernadat,[†] Bruno Figadère,[†] and Laurent Ferrié*[,†]

[†]BioCIS, Université Paris-Sud, CNRS, Université Paris-Saclay, Chatenay-Malabry 92290, France

[‡]Institute of Marine Biochemistry, Vietnam Academy of Science and Technology (VAST), Cau Giay, Hanoi, Vietnam

Supporting Information

ABSTRACT: The synthesis of acetoxyendoperoxyacetal derivatives allowed the formation of functionalized 3,5-disubstituted 1,2-dioxolanes through the formation of reactive peroxycarbenium species under Lewis acid mediation. The introduction of a neutral nucleophile such as allylsilane, silane, or silyl enol ether was accomplished with moderate to good yields. The two studied Lewis acids, $TiCl_4$ and $SnCl_4$, gave contrasting results. The higher diastereoselectivity toward the *trans* diastereomer in experiments with $TiCl_4$ as Lewis acid was explained by a faster degradation of the *cis* isomer product, leading generally to lower yields. A rationalization of this result was supported by calculations.



Organic peroxides are uncommon moieties for natural products.[1] Nevertheless, this pharmacophore is often a source of potent biological properties due to the relative reactivity of peroxides. In addition to the famous antimalarial agent, artemisinin, isolated from *Artemesia annua* plant,[2] many other organisms produce peroxide-containing natural products. In particular, plakinic acids, isolated from sponges *Plakortis* sp., exhibit a fatty acid structure with a 1,2-dioxolane ring between positions 3 and 5 (Figure 1).[3] Another characteristic of plakinic acids is that the 1,2-dioxolane ring is 3,3,5,5-tetrasubstituted. More recently, we investigated the synthesis of simpler analogues of mycangimycin,[4] a new peroxide isolated from *Streptomyces* sp. living in symbiosis with the insect *Dendroctonus frontalis*.[5] Mycangimycin has a very similar structure compared to plakinic acids, but besides its highly conjugated fatty chain, the 1,2-dioxolane ring is only 3,5-disubstituted (Figure 1). This difference in the structure is detrimental for the synthesis of this compound. Indeed, the substitution pattern present in the dioxolane ring of plakinic acids facilitates the preparation of such compounds due to the enhanced stabilization of intermediate carbenium or radical species necessary to provide the expected structure.[6] Precursors of 3,5-tetrasubstituted dioxolane rings can also be double bonds though peroxymercuration,[7] and here again, the substitution of starting olefins for mycangimycin derivatives is detrimental to the reactivity of the required olefin. For these reasons, relatively few examples of the preparation of 3,5-disubstituted 1,2-dioxolanes are found in the literature.[6]

Peroxycarbenium ions have emerged as a powerful tool for the synthesis of organic peroxides.[8] Nevertheless, the synthesis of 3,5-disubstituted 1,2-dioxolanes from the corresponding peroxyacetals is still an issue due to a reduced stabilization of the peroxycarbenium ion as intermediate. Moreover, a disfavored withdrawing effect by induction of one oxygen atom to the other at the peroxide moiety reduces the ability to stabilize the peroxycarbenium compared to a classical acetal. Indeed, we planned to use in early experiments some reported

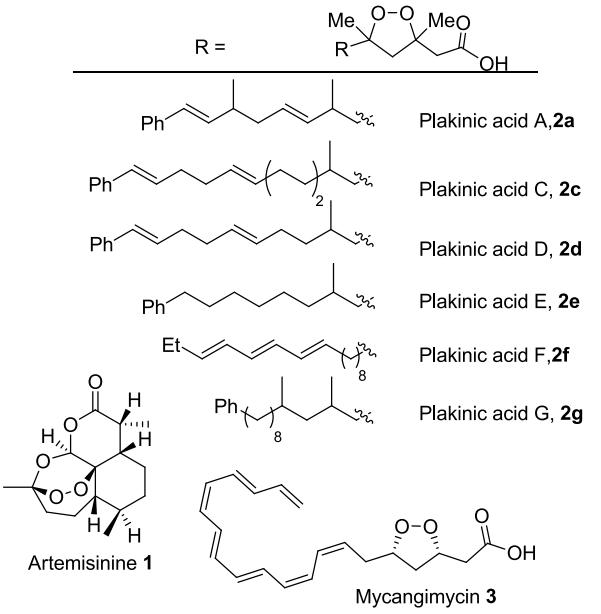


Figure 1. Artemisinin, plakinic acids, and mycangimycin.

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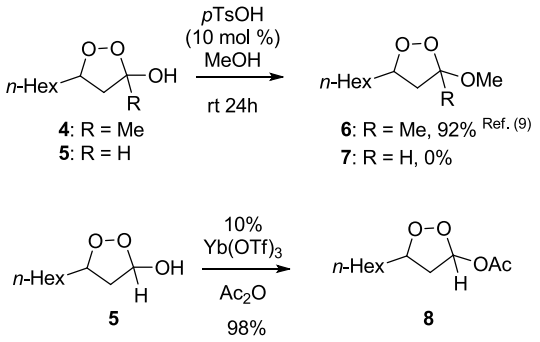
methodologies from Dussault et al.[8b] to perform the nucleophilic addition to peroxyacetal such as methoxyperoxyketal **6**, which has been prepared from hemiperoxyketal **4** by acid-mediated metathesis with MeOH.[9] However, to our disappointment, we were unable to prepare entity **7** from hemiperoxyacetal **5** (prepared from cyclopropanol by oxidative ring opening with triplet oxygen, see the Supporting Information) and any simple alcohol. By analogy with tetrahydrofurans, we decided to activate the cyclic peroxyacetal as acetate due to its known excellent leaving group ability (Scheme 1).

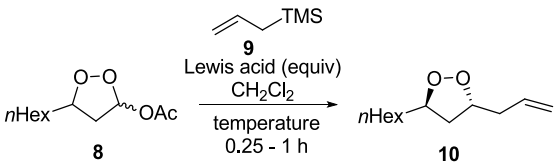
Scheme 1. Activation of Endoperoxy Ketals and Acetals



In the first attempts, we experienced issues in obtaining acetate **8** under classical conditions involving pyridine and Ac_2O, but only decomposition was observed, which can explain why a similar structure was scarcely reported.[10] Fortunately, the preparation of such a compound was possible by using Lewis acid catalyzed acetylation conditions. With rare earth triflates such as $Yb(OTf)_3$, we obtained expected acetate **8** in high yield. It is worth noting that stability of this compound is pretty high compared to THF acetate derivatives due to a reduced stabilization of the peroxycarbenium compared to THF oxycarbeniums, and thus, compound **8** can then be generally purified by flash chromatography on silica gel without notable decomposition (Scheme 1).

A Sakurai reaction between peroxyacetal **8** and allyltrimethylsilane **9** was then investigated in the search for optimized reaction conditions. Dichloromethane was found to be the most suited solvent for this reaction. TMSOTf or $BF_3{\cdot}OEt_2$ was an ineffective promoter for this transformation, converting only small amounts of starting material (Table 1, entries 1 and 2). In contrast, $SnCl_4$ and $TiCl_4$ were far more promising. Indeed, $SnCl_4$ gave a high isolated yield of dioxolane **10** (Table 1, entry 4) at −40 °C. At lower temperature (entry 3), the reaction hardly proceeded with recovery of starting material after 1 h. The extended reaction time did not significantly improve the yield and/or the diastereoselectivity. At higher temperature, the yields also decreased due to some degradation (Table 1, entries 5 and 6). The observed diastereoselectivity is moderated, in contrast to those observed on 2,4-disubstituted THF derivatives.[11] This limited selectivity could be attributed to a competition between two conformers of the peroxycarbenium species. We also turned our attention to $TiCl_4$; similar to $SnCl_4$, the reaction must be conducted at −40 °C (Table 1, entry 8) rather than −78 °C (Table 1, entry 7). However, in contrast to $SnCl_4$, diastereoselectivity for 1,2-dioxolane **10** was largely improved up to 85:15, albeit with a lower yield. To explain this enhancement, we suspected reaction product **10** to

Table 1. Screening of Lewis acid, Stoichiometry, And Temperature on the Sakurai Reaction between Acetoxy Peroxyketal 8 and AllylTMS 9



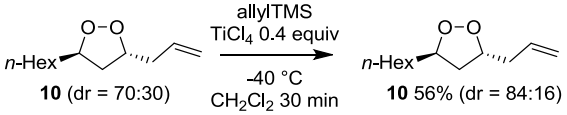
entry	Lewis acid	equiv	temp (°C)	yield[a] (%)	dr[b] (*trans*/*cis*)
1	TMSOTf	0.1 or 1	−78 to rt	<10	nd[c]
2	$BF_3{\cdot}OEt_2$	1.0	−78 to rt	19	nd[c]
3	$SnCl_4$	0.9	−78	13[d]	50:50
4	$SnCl_4$	0.9	−40	80	65:35
5	$SnCl_4$	0.9	0	31	78:22
6	$SnCl_4$	1.0	rt	*e*	*e*
7	$TiCl_4$	0.9	−78	7[d]	75:25
8	$TiCl_4$	0.9	−40	47	85:15
9	$TiCl_4$	1.1	−40	30	91:9
10	$TiCl_4$	0.7	−40	60	70:30

[a]Isolated yield. [b]Diastereomeric ratios were determined by ^{1}H NMR. [c]Not determined. [d]50% of recovered starting material. [e]Decomposition.

endure a selective degradation of the *cis* isomer, therefore enriching the proportion of *trans* isomer but decreasing overall yield. Indeed, this hypothesis was confirmed by adjusting the number of equivalents of $TiCl_4$ to the reaction mixture. Increasing the stoichiometry of $TiCl_4$ to 1.1 equiv decreased the yield but increased the diastereoselectivity to 91:9 (Table 1, entry 9), while decreasing the amount of $TiCl_4$ to 0.7 equiv improved the yield but decreased the diastereoselectivity of **10** to 70:30 (Table 1, entry 10).

An additional experiment allowed us to confirm our hypothesis by applying Sakurai reaction conditions to dioxolane **10** with a reduced amount of $TiCl_4$ (0.4 equiv). After 30 min, the reaction mixture was quenched and purified to afford starting material in 56% recovered yield but with an improved diastereoselectivity in favor of the *trans* compound (from 70:30 to 84:16, Scheme 2).

Scheme 2. Partial Degradation of Dioxolane 10 Using a Reduced Amount of $TiCl_4$ under the Reaction Conditions of a Sakurai Reaction



The mechanism of this $TiCl_4$-catalyzed degradation was further investigated, and some major degradation products were identified. A $TiCl_4$-catalyzed Kornblum−DeLaMare rearrangement[12] of dioxolane **10** afforded compounds **12** and **13** on one hand (Scheme 3, top route). On the other hand, $TiCl_4$-mediated fragmentation of dioxolane **10** also afforded aldehyde **14** and ketone **15** from intermediate **11a**. Under Sakurai reaction conditions, a reactive species such as aldehyde **14** was converted into allyl adduct **18** (Scheme 3, bottom route). Presumably, a similar process occurred from intermediate **11b** as well, but the expected degradation

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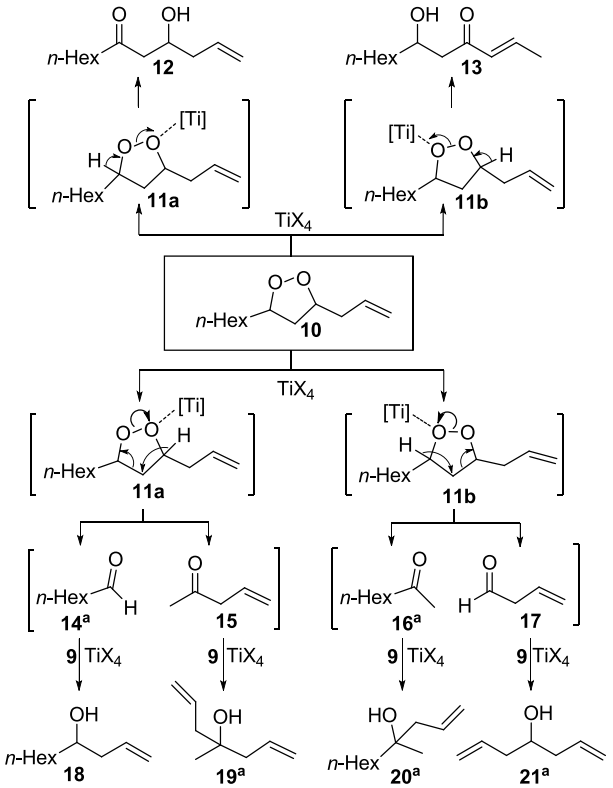
Scheme 3. Identification of $TiCl_4$-Mediated Degradation Products of Dioxolane 10



[a]Not isolated but observed by GC/MS.

products were not produced in sufficient amounts, and also due to the relative volatility for some of them, side products **14**, **16**, **19**, **20**, and **21** were only observed from GC/MS analysis of the crude material and were not isolated. The mechanism of this fragmentation is not completely clear on our system, since the possibility of a retro-aldol reaction from 1,3-hydroxyketones **12** and **13** cannot be completely excluded. However, a similar fragmentation was studied on 3,3,4-trisubstituted 1,2-dioxolanes with $TiCl_4$, affording ketones and aldehydes with migration of an alkyl group, an hydrogen, or a deuterium.[13] An analogous fragmentation was also observed in one of our previous works, where a bicyclic peroxyketal afforded a ketoester under triflic acid activation.[4] These two examples show that a retro-aldol process might not occur since it cannot explain the formed product. Here, the migration of the proton from position 3 or 5 to position 4 of the 1,2-dioxolane ring is probably concomitant with the peroxide bond and carbon−carbon bond cleavage (Scheme 3).

The origin of the enhancement of the diastereoselectivity by degradation in the presence of $TiCl_4$ in favor of a *trans* compound was then investigated at the B3LYP/(6-31+G(d,p), LanL2DZ)[14] level of theory (Pople's basis set for organoelements and Los Alamos effective core potential for metallic centers). We focused our study on one of the two possible $TiCl_4$-mediated Kornblum−DeLaMare rearrangements, leading to intermediate **23** from dioxolane **22**, a simplified model of dioxolane **10** (Figure 2). Transition states starting from diastereoisomers *cis*-**22** and *trans*-**22** were localized on the potential energy surface. First attempts to search a pathway for the transition state from *cis/trans*-**22** and $TiCl_4$ only were unsuccessful. Introduction of a proton acceptor under the form

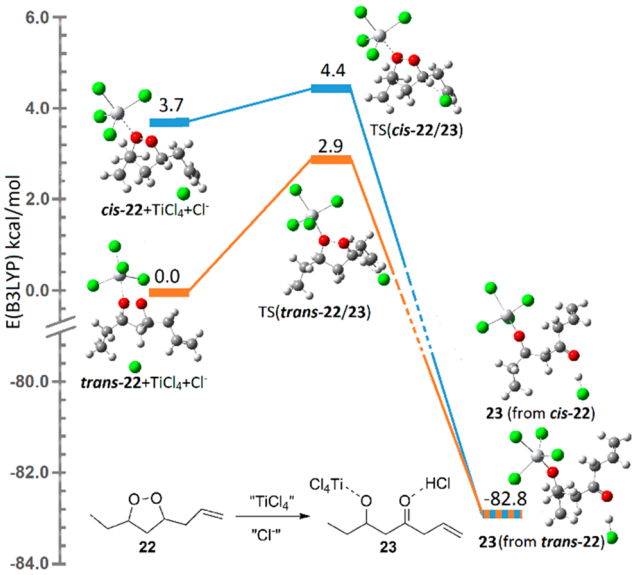


Figure 2. Energy profiles of the $TiCl_4$-mediated Kornblum−DeLaMare rearrangements of model compound *cis*- and *trans*-**22** at the B3LYP/(6-31+G(d,p), LanL2DZ) level of theory. Electronic energy along the coordinates is represented in kcal/mol relative to [*trans*-**22** + $TiCl_4$ + Cl^-]. A chloride anion was used as a base to scavenge the proton freed in the reaction.

of an additional chloride anion, which is likely to be found in the reaction medium, allowed the rearrangement to occur. The difference of activation energy $\Delta\Delta E^{\ddagger}$ between the two diastereomers was found to be 2.2 kcal/mol, in favor of isomer *cis*-**22**. This result is consistent with our observation of a faster degradation of *cis*-**10** compared to *trans*-**10** with $TiCl_4$ and subsequent enrichment of this latter. The energy for [*cis*-**22** + $TiCl_4$ + Cl^-] is higher by 3.7 kcal/mol compared to the *trans* isomer, probably due to steric interactions between the two alkyl groups at the backside of the 1,2-dioxolane ring, squeezed by $TiCl_4$ and chlorine placed on the front face. In contrast, the transition state for *cis*-**22** is only 0.7 kcal/mol higher due to the free field for proton trapping by chlorine anion at the front face of the dioxolane ring. In the meantime, a steric congestion exists between chlorine and one alkyl group in the transition state for *trans*-**22**, demanding more energy (2.9 kcal/mol) to perform the reaction (Figure 2).

We then turned our attention to the nature of the nucleophile being able to react on endoperoxyacetal **8**. The use of various allylsilanes proved to be successful (Table 2, entries 1−6). The selective degradation of *cis* diastereoisomer with $TiCl_4$ gave always better *trans* selectivity. Silyl enol ethers were also screened as potent nucleophiles (Table 2, entries 7−10). The *cis* diastereoisomer was obtained as major product, although $TiCl_4$ mitigated this result due to a selective degradation of *cis* diastereoisomer. Cyanide **29** was a very effective nucleophile with $SnCl_4$ as well as azide **30**, giving the expected products **37** and **38** with excellent yields but no control of the diastereoselectivity. $TiCl_4$ was not able to improve this result, resulting only in decreased yield (Table 2, entries 11−13). Reduction of the endoperoxyacetal is also possible with triethylsilane **31**, producing 3-monosubstituted dioxolane **39** (entries 14 and 15).

Next, we explored substrates **40**−**46** (easily obtained as compound **8**, see the Supporting Information) in the Sakurai reaction with allylsilane **9**. In order to improve the

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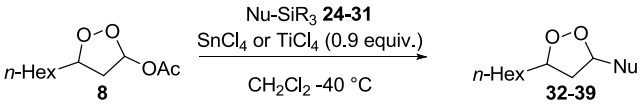
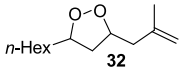
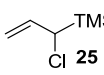
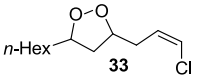
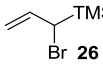
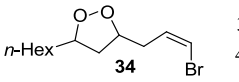
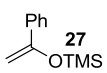
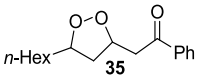
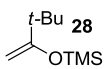
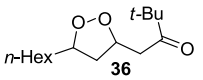
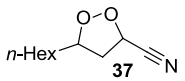
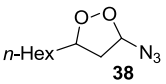
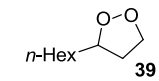
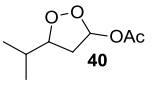
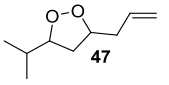
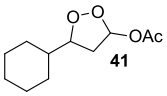
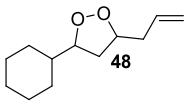
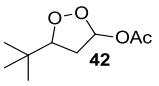
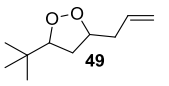
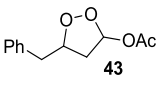
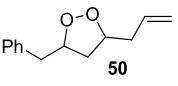
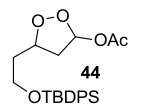
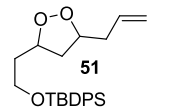
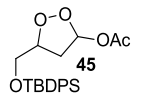
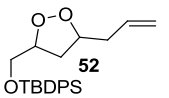
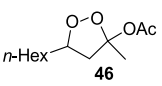
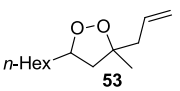
Table 2. Addition of Various Nucleophiles to Peroxyacetal 8[a]



entry	Nu-SiR$_3$	Lewis acid	product	yield (%)[b] (dr *trans*:*cis*)[c]
1	 **24**	$SnCl_4$	 **32**	79 (40:60)
2		$TiCl_4$		15 (75:25)
3	 **25**	$SnCl_4$	 **33**	38 (80:20)[d]
4		$TiCl_4$		41 (83:17)[d]
5	 **26**	$SnCl_4$	 **34**	30 (80:20)[e]
6		$TiCl_4$		40 (92:08)[e]
7	 **27**	$SnCl_4$	 **35**	70 (35:65)
8		$TiCl_4$		43 (43:57)
9	 **28**	$SnCl_4$	 **36**	77 (40:60)
10		$TiCl_4$		16 (50:50)
11	TMS-CN **29**	$SnCl_4$	 **37**	87 (50:50)
12	TMS-N$_3$ **30**	$SnCl_4$	 **38**	78 (50:50)
13		$TiCl_4$		32% (50:50)
14	Et$_3$Si-H **31**	$SnCl_4$	 **39**	66
15		$TiCl_4$		79

[a]Reaction conditions: **8** (1 equiv), $TiCl_4$, or $SnCl_4$ (0.9 equiv), nucleophile **24**–**31** (3 equiv). [b]Isolated yield. [c]Diastereomeric ratios were determined by ^{1}H NMR. [d]*E*/*Z* ratio = 1:4 (^{1}H NMR). [e]*E*/*Z* ratio = 1:2 (^{1}H NMR).

Table 3. Use of Various Peroxyacetals 40–45 and Peroxyketal 46 in the Sakurai Reaction with Allyltrimethylsilane 9[a]

entry	substrate	Lewis acid	product	yield (%)[b] (dr *trans*:*cis*)[c]
1	 **40**	$SnCl_4$	 **47**	30 (60:40)
2		$TiCl_4$		35 (80:20)
3	 **41**	$SnCl_4$	 **48**	91 (60:40)
4		$TiCl_4$		28 (85:15)
5	 **42**	$SnCl_4$	 **49**	92 (60:40)
6		$TiCl_4$		95 (60:40)
7	 **43**	$SnCl_4$	 **50**	87 (50:50)
8		$TiCl_4$		32 (85:15)
9	 **44**	$SnCl_4$	 **51**	82 (70:30)
10		$TiCl_4$		33 (83:17)
11	 **45**	$SnCl_4$	 **52**	59 (50:50)
13	 **46**	$SnCl_4$	 **53**	38 (75:25)[d]
14		$TiCl_4$		20 (90:10)[d]

[a]Reaction conditions: **40**–**46** (1 equiv), $TiCl_4$ or $SnCl_4$ (0.9 equiv), allyltrimethylsilane (3 equiv) in CH_2Cl_2 at −40 °C. [b]Isolated yield. [c]Diastereoselectivities were determined by ^{1}H NMR. [d]Yield calculated over two steps from hemiperoxyketal precursor of acetate **46**.

diastereoselectivity of the reaction, bulky dioxolanyl acetates **40**–**42** were studied (Table 3, entries 1–6). Unfortunately, these substrates did not improve the diastereoselectivity compared to acetate **8** (Table 1), and a selective degradation of *cis* product was still observed when $TiCl_4$ was used in most of the cases. Nevertheless, high steric congestion of the *tert*-butyl group for compound **42** seemed to suppress degradation of product **49**, affording a high yield of it using both Lewis acids. Benzyl-substituted and protected alcohols are compatible in this reaction, leading to good yield with $SnCl_4$ and improved *trans* diastereoselectivity with $TiCl_4$, as expected (Table 3, entries 7–11). Ketal derivative **46** was also examined with our protocol (Table 3, entries 13 and 14). Due to the improved stabilization of the peroxonium species with the methyl group, compound **46** proved to be unstable and could not be isolated cleanly. The crude material was used directly in the Sakurai reaction, meaning that the yield was calculated over two steps. Product **53** was obtained with good selectivity with both $SnCl_4$ and $TiCl_4$. This result is comparable in yield (over two steps) with Dussault's procedure, meaning our methodology is not only limited to endoperoxyacetals.[7,15]

In conclusion, we developed a new method for the formation of 3,5-disubstituted 1,2-dioxolanes through the use of acetoxy peroxyacetals and the formation of peroxycabenium intermediate species under $SnCl_4$ or $TiCl_4$ activation. The formation of acetoxy peroxyacetal by using a Lewis acid catalysis proved to be essential for their formation and allowed sufficient reactivity for further functionalization. $SnCl_4$ and $TiCl_4$ were found to be the best Lewis acids screened so far. A wide variety of substrates and nucleophiles were compatible with the reaction conditions. A variety of results were observed between these two reagents: $SnCl_4$ generally gave good yields but moderate selectivities, while $TiCl_4$ furnished higher selectivity toward the *trans* products but generally lower yields. In this case, a $TiCl_4$-mediated decomposition of the newly formed products takes place, where the *cis*-disubstituted dioxolane seems to decompose faster than the *trans* isomer, explaining the improved selectivities and lower yields thus observed. Calculation about toward one degradation pathway could rationalize why *cis*-1,2-dioxolanes decompose more easily under treatment with $TiCl_4$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01616.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of new compounds (including precursors such as cyclopropanols, 1,2-dioxolanols, and

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dioxolanyl acetates); Cartesian coordinates of compounds *cis*-**22**, *trans*-**22**, **23** and their transition states (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: laurent.ferrie@u-psud.fr.

ORCID

Guillaume Bernadat: 0000-0001-8955-0364
Bruno Figadère: 0000-0003-4226-8489
Laurent Ferrié: 0000-0002-1171-205X

Notes

The authors declare no competing financial interest.

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