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Iron- and Indium-Catalyzed Reactions toward Nitrogen- and Oxygen-Containing Saturated Heterocycles

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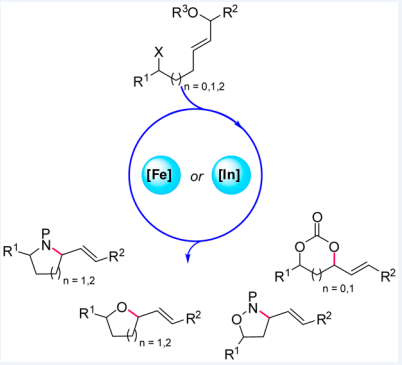
CONSPECTUS: A myriad of natural and/or biologically active products include nitrogen- and oxygen-containing saturated heterocycles, which are thus considered as attractive scaffolds in the drug discovery process. As a consequence, a wide range of reactions has been developed for the construction of these frameworks, much effort being specially devoted to the formation of substituted tetrahydropyrans and piperidines. Among the existing methods to form these heterocycles, the metal-catalyzed heterocyclization of amino- or hydroxy-allylic alcohol derivatives has emerged as a powerful and stereoselective strategy that is particularly interesting in terms of both atom-economy and ecocompatibility. For a long time, palladium catalysts have widely dominated this area either in Tsuji−Trost reactions [Pd(0)] or in an electrophilic activation process [Pd(II)]. More recently, gold-catalyzed formation of saturated *N*- and *O*-heterocycles has received growing attention because it generally exhibits high efficiency and diastereoselectivity. Despite their demonstrated utility, Pd- and Au-complexes suffer from high costs, toxicity, and limited natural abundance, which can be barriers to their widespread use in industrial processes. Thus, the replacement of precious metals with less expensive and more environmentally benign catalysts has become a challenging issue for organic chemists.



In 2010, our group took advantage of the ability of the low-toxicity and inexpensive $FeCl_3$ in activating allylic or benzylic alcohols to develop iron-catalyzed *N*- and *O*-heterocylizations. We first focused on *N*-heterocycles, and a variety of 2,6-disubstituted piperidines as well as pyrrolidines were synthesized in a highly diastereoselective fashion in favor of the *cis*-compounds. The reaction was further extended to the construction of substituted tetrahydropyrans. Besides triggering the formation of heterocycles, the iron salts were shown to induce a thermodynamic epimerization, which is the key to reach the high diastereoselectivities observed in favor of the most stable *cis*-isomers. It is worth noting that spiroketals could be prepared by using this method, which was successfully applied to a synthetic approach toward natural products belonging to the bistramide family. We then turned our attention to heterocycles incorporating two heteroatoms such as isoxazolidines. These frameworks can be found in biologically active natural products, and in addition, they can be transformed into 1,3-amino alcohols, which are of importance in organic chemistry. The use of $FeCl_3{\cdot}6H_2O$ allowed the access to a large variety of 3,5-disubstituted isoxazolidines from *δ*-hydroxylamino allylic alcohol derivatives with good yields and diastereoselectivities in favor of the *cis*-isomer. Recently, a Lewis acid-catalyzed synthesis of six- and five-membered ring carbonates starting from linear *tert*-butyl carbonates was reported. In some cases, the mild and chemoselective $InCl_3$ was preferred over $FeCl_3{\cdot}6H_2O$ to avoid side-product formation. The resulting cyclic carbonates were easily transformed into 1,3- or 1,2-diols, and a total synthesis of (3*S*,5*S*)-alpinikatin was achieved.

1. INTRODUCTION

Over the past decade, a growing interest has been devoted to the development of ecofriendly, inexpensive, and low-polluting chemical processes.[1] Metal-catalyzed activation of allylic alcohols meets these requirements in terms of both sustainability and atom-economy, because water is the only byproduct formed during the reaction with a nucleophile.[2] In an intramolecular fashion, this method emerged as an attractive strategy to form pharmaceutically relevant heterocycles such as polysubstituted piperidines and tetrahydropyrans **B** from *ζ*-amino- or *ζ*-hydroxy-allylic alcohol derivatives of type **A** (Scheme 1).

In this area, the electrophilic Pd(II) catalysts have been prevalent for a long time. In 1994, Hirai and Nagatsu were the first to describe a Pd(II)-catalyzed heterocyclization of an amino allylic alcohol derivative, **I-1**, delivering the corresponding piperidine, **I-2**, which was the precursor of (+)-coniine (Scheme

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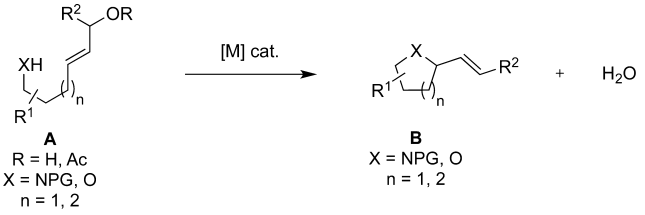
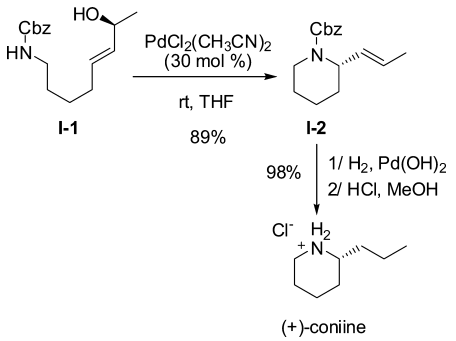
Scheme 1. Cyclization of Allylic Alcohol or Acetate Derivatives A to Heterocycles B



2).[3] The enantioselectivity of the reaction resulted from a 1,3-chirality transfer. This asymmetric induction was further deeply

Scheme 2. Pioneering Work of Hirai and Nagatsu[3]

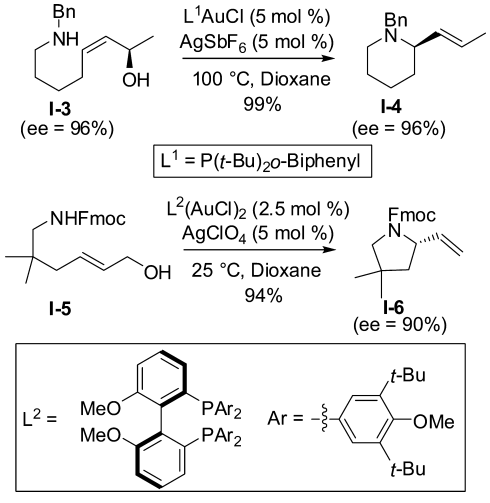


investigated 15 years later, and a hypothetical mechanism involving a *syn*-azapalladation and a final *syn*-elimination was proposed to account for the stereochemical outcome of the cyclization.[4] This method was successfully applied to the synthesis of numerous polysubstituted piperidines that were transformed into natural or bioactive products.[5]

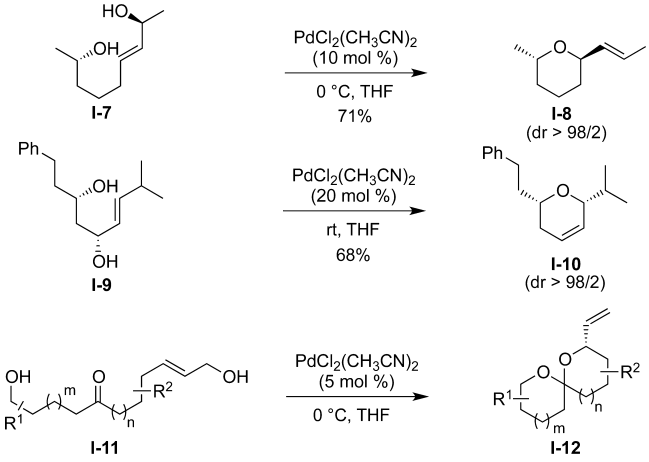
More recently, enantioselective gold-catalyzed amination of allylic alcohols such as **I-3** and **I-5** were reported providing five- and six-membered ring *N*-heterocycles **I-4** and **I-6** (Scheme 3).[6]

The oxygenated version of these metal-catalyzed heterocyclizations was studied, and under Pd(II) catalysis, tetrahydropyrans **I-8**, as well as dihydropyrans **I-10** and spiroketals **I-12**, were obtained from allylic alcohols in high yields and diastereoselectivities (Scheme 4).[7]

Scheme 3. Au(I)-Catalyzed Formation of N-Heterocycles

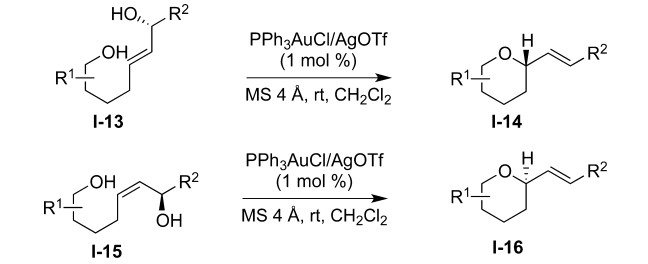


Scheme 4. Pd(II)-Catalyzed Cyclization of Oxygenated Compounds



In 2008, gold catalysis entered this research field and a cationic gold complex was shown to promote the cyclization of monoallylic diols **I-13** and **I-15** via a hypothesized S_N2' pathway. An enantioselective reaction relying on a 1,3-chirality transfer was developed allowing the specific formation of an enantiomer according to the geometry of the double bond (Scheme 5).[8]

Scheme 5. Gold-Catalyzed Synthesis of Tetrahydropyrans



Despite their demonstrated utility in metal-catalyzed heterocyclization, Pd(II) and Au(I) catalysts and their associated ligands suffer some drawbacks such as high cost, human toxicity, and limited natural abundance.[9] These issues could explain the renewed interest that has been dedicated to iron catalysis over the past 10 years.[10] Particularly, cheap and benign iron salts were found to efficiently activate allylic or benzylic alcohols toward the addition of various nucleophiles, including *N*- and *O*-nucleophiles, mostly in intermolecular reactions.[11]

Focusing on the ecofriendly synthesis of pharmaceutically relevant scaffolds, our group embarked on the development of iron-catalyzed heterocyclizations of allylic alcohol derivatives. A diastereoselective $FeCl_3 \cdot 6H_2O$-catalyzed synthesis of substituted piperidines and tetrahydropyrans was described.[12] The same catalyst was used to prepare five-membered ring *N*-heterocycles.[13] A few years later, a similar catalytic system was used to form isoxazolidines[14] and cyclic carbonates,[15] which are precursors of amino alcohols and diols, respectively. In this Account, our contribution in the field of Lewis acid-catalyzed heterocyclization is reported.

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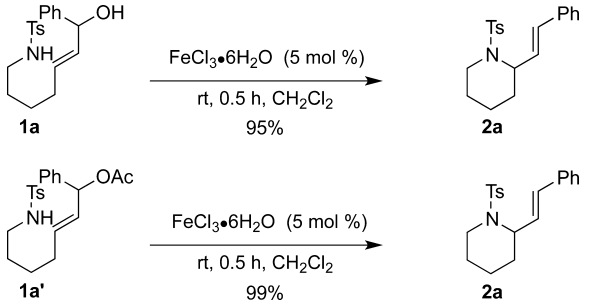
2. IRON-CATALYZED FORMATION OF *N*-HETEROCYCLES

2.1. Synthesis of Piperidines[12a]

In 2010, we reported access to piperidines from N-protected ζ-amino alcohol derivatives in the presence of a catalytic amount of $FeCl_3 \cdot 6H_2O$.[16] We initiated our studies by using a tosylamide as the nucleophile, and pleasingly, the cyclization took place smoothly providing the corresponding monosubstituted piperidine **2a** in an excellent 95% yield (Scheme 6). The hydroxyl

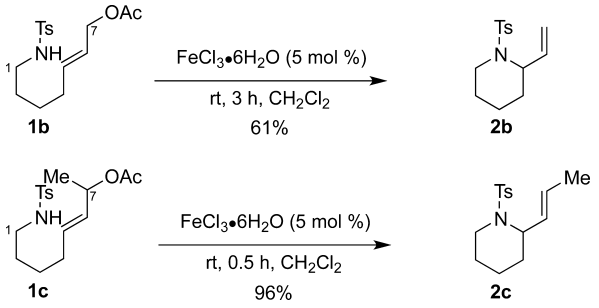
Scheme 6. Cyclization of *N*-Tosylamides



group could be changed for an acetate without affecting the yield, and due to synthetic issues, amino acetates were preferred to evaluate the scope of the reaction.

The allylic substituent at C7 was found to be critical: in the absence of any group in this position, the reaction turned sluggish providing the expected piperidine **2b** with a moderate 61% yield. In contrast, when a methyl group was introduced, the reactivity was restored, and **2c** was isolated in high yield (96%) (Scheme 7).

Scheme 7. Influence of the Allylic Substituent at C7



When the *N*-tosyl group was replaced by a carbamate (PG = Boc, Cbz), the corresponding piperidines **2d** and **2e** were delivered, albeit in a slightly lower yield (72% and 65%, respectively, versus 99% in the case of the *N*-tosyl moiety) (Scheme 8).

The reaction was generalized to the synthesis of 2,6-disubstituted piperidines from 1-substituted (*E*)-unsaturated amino acetates. The cyclization of *N*-tosylamides was first examined, and interestingly, in the presence of a linear pentyl side chain at C1, the 2,6-disubstituted piperidine was isolated in good yield (70%) and in high diastereoselectivity (dr = 97:3) in favor of the *cis*-isomer (Table 1, entry 1). The result was better with an isopropyl substituent at C1 because only one diastereomer was formed (dr > 99:1) in quantitative yield (Table 1, entry 2). Even when a poorly sterically demanding methyl substituent was introduced, the cyclization furnished the *cis*-2,6-disubstituted

Scheme 8. Cyclization of *N*-Carbamates

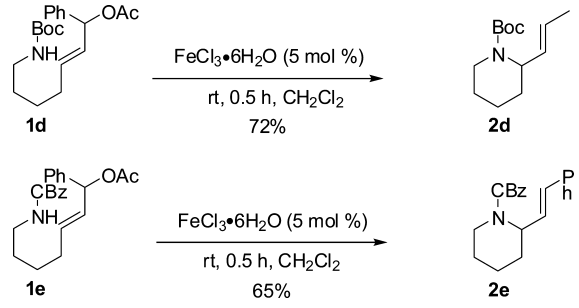
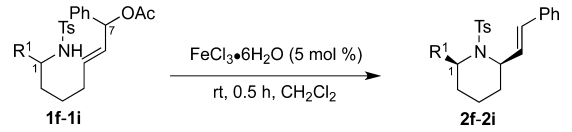


Table 1. Formation of 2,6-Substituted Piperidines from *N*-Tosylamides



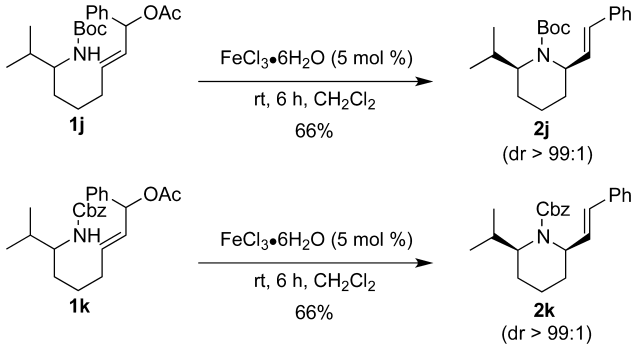
entry	R^1	1	2	yield (%)	*cis*/*trans*[a]
1	*n*-C_5H_{11}	**1f**	**2f**	70	97:3
2	*i*Pr	**1g**	**2g**	99	>99:1
3	Me	**1h**	**2h**	80	92:8
4	Ph	**1i**	**2i**	80	90:10

[a]Determined by ^{1}H NMR.

piperidine in a good diastereomeric ratio (dr = 92:8) (Table 1, entry 3). A phenyl substituent was also tolerated showing that the R^1 group at C1 has a low influence on the outcome of the cyclization (Table 1, entry 4).

When *N*-carbamates were used, the corresponding 2,6-disubstituted piperidines were isolated as single *cis*-diastereomers with a moderate yield of 66%, which was comparable to those obtained in the case of monosubstituted piperidines (Scheme 9).

Scheme 9. Formation of 2,6-Substituted Piperidines from *N*-Carbamates



An interesting result was observed when the *N*-nosyl derivative **1l** was reacted with $FeCl_3 \cdot 6H_2O$ (5 mol %) because, after 2 h, piperidine **2l** was formed with an excellent yield (90%) although with no diastereoselectivity (dr = 50:50). However, the *cis*-product could be produced exclusively (dr > 99:1) by increasing the catalytic loading to 10 mol % and the reaction time (10 h). A similar result was obtained starting from a 50:50 mixture of *cis*-**2l** and *trans*-**2l** under the same conditions [$FeCl_3 \cdot 6H_2O$ (10 mol %), 10 h], thus suggesting an iron-induced epimerization of the *N*-heterocycle (Scheme 10).

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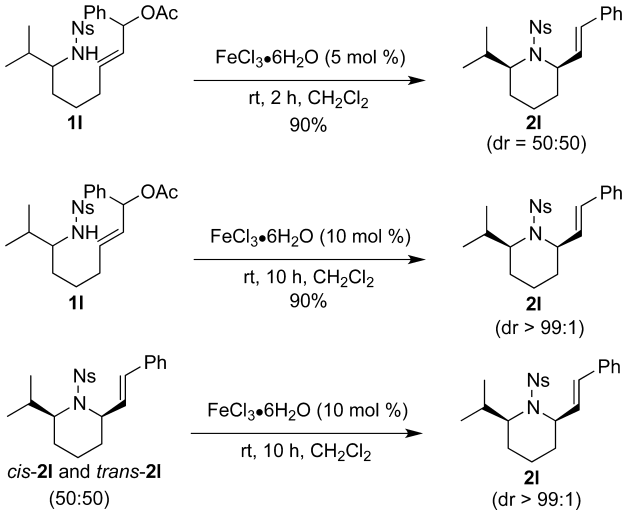
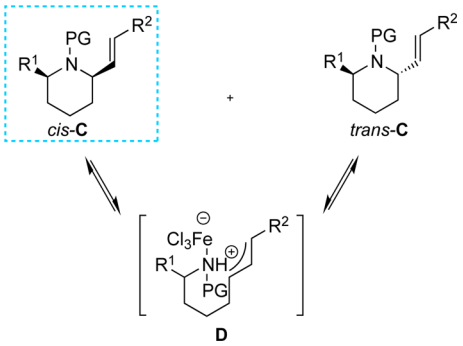
Scheme 10. Cyclization of *N*-Nosylamides



The observed epimerization of the piperidine could result from an iron-catalyzed reopening of the heterocycle via a zwitterionic intermediate **D**. Due to this reopening, a thermodynamic equilibrium takes place leading to the more stable *cis*-diastereomer (Scheme 11).

Scheme 11. $FeCl_3$-Induced Epimerization of 2,6-Disubstituted Piperidines

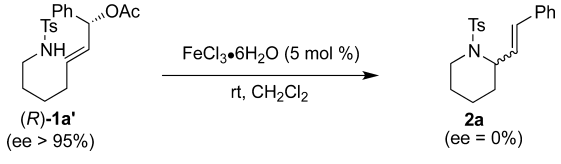


In order to confirm the formation of a carbocationic intermediate, the optically active acetate (*R*)-**1a**′ was treated with $FeCl_3 \cdot 6H_2O$ (5 mol %). As expected, the corresponding piperidine was obtained as a racemate thus underlining the loss of the stereochemical information during the process (Scheme 12). This hypothesized mechanism strongly differs from those proposed for the Pd(II)- or Au(I)-catalyzed cyclizations.[3−6]

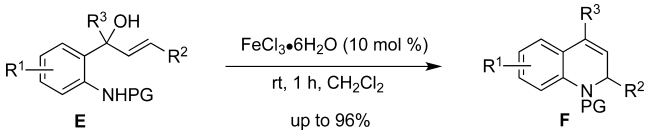
2.2. Formation of Dihydro- and Tetrahydro-(iso)quinolines

In 2012, Sun and co-workers reported the iron-catalyzed synthesis of substituted dihydroquinolines of type *F* from 2-aminophenyl-1-en-3-ol derivatives *E* (Scheme 13).[17,18]

Scheme 12. Absence of 1,3-Chirality Transfer



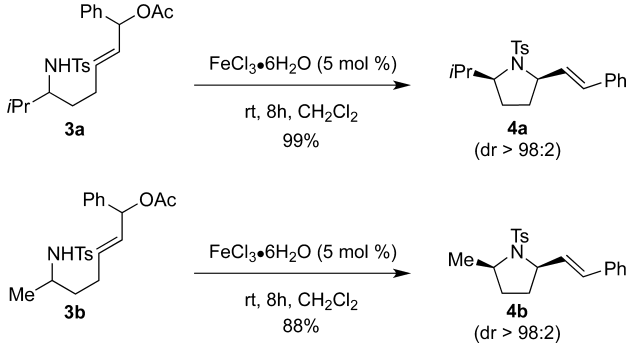
Scheme 13. Iron-Catalyzed Synthesis of Dihydroquinolines



2.3. Formation of Pyrrolidines[13]

The iron-catalyzed cyclization was used for the synthesis of five-membered ring *N*-heterocycles from *δ*-amino allylic acetate derivatives. The method proved to be efficient and highly diastereoselective furnishing 2,5-disubstituted pyrrolidines **4a** and **4b** as single *cis*-diastereomers (Scheme 14).[19]

Scheme 14. Iron-Catalyzed Formation of Pyrrolidines

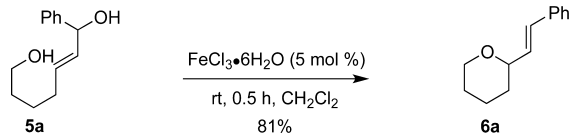


3. IRON-CATALYZED FORMATION OF *O*-HETEROCYCLES

3.1. Synthesis of Tetrahydropyrans[12]

$FeCl_3 \cdot 6H_2O$ was also found to be effective for the formation of tetrahydropyrans from monoallylic diols. The cyclization of **5a** proceeded smoothly in only 30 min delivering the expected monosubstituted tetrahydropyran **6a** in a good yield (81%) (Scheme 15).

Scheme 15. Formation of a Mono-Substituted Tetrahydropyran



The diastereoselectivity of the reaction was investigated, and pleasingly, 2,6-disubstituted tetrahydropyrans **6b** and **6c**, possessing a pentyl or an ester substituent, were isolated in good yields and with high diastereoselectivity in favor of the *cis*-isomer.[20] The chemoselectivity of the reaction was well demonstrated by the quantitative formation of **6c**, which incorporated an ester moiety even though, in this case, an additional amount of the iron catalyst as well as additionnal reaction time was needed to reach a good diastereomeric ratio (Scheme 16).

A range of allylic substituents (R^2 = Ph, Mes, Me) were tolerated under the reaction conditions, and in all cases, excellent diastereoselectivities were observed. A tertiary allylic alcohol could be used as the leaving group (R^2 = R^3 = Me), thus

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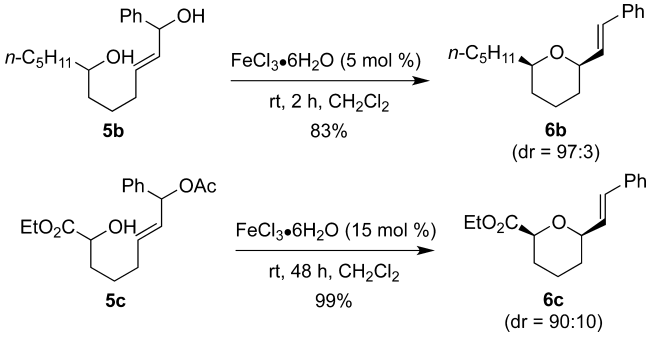
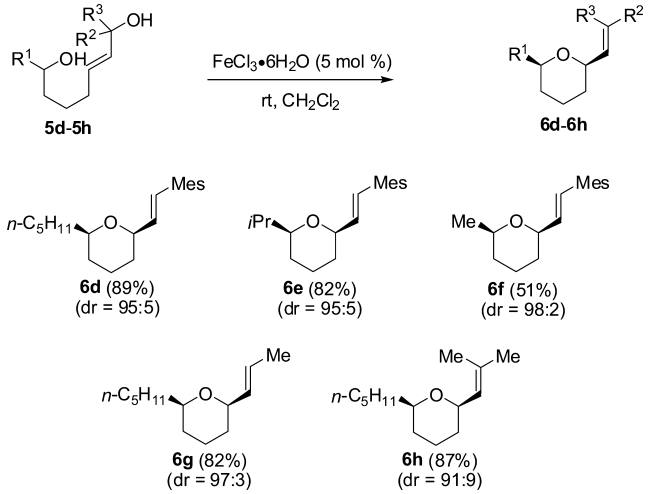
Scheme 16. Formation of 2,6-Disubstituted Tetrahydropyrans



delivering tetrahydropyran **6h** possessing a trisubstituted double bond (Scheme 17).[21]

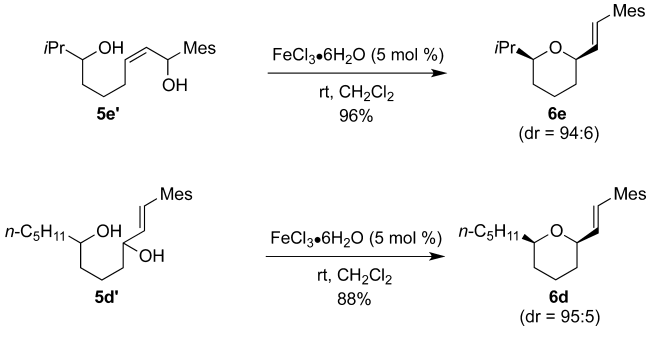
Scheme 17. Influence of the Allylic Substituent



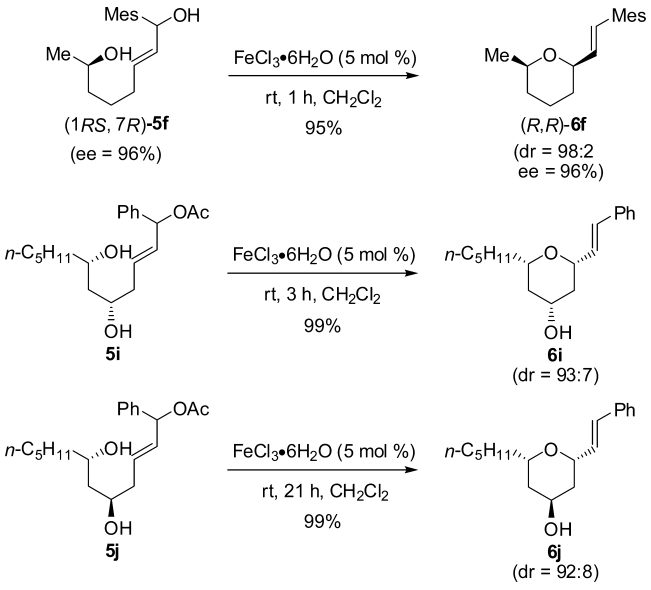
The geometry of the double bond in the linear substrate showed no influence on the outcome of the cyclization, and the allylic hydroxyl leaving group could be moved to the ε-position without affecting the yield of the reaction (Scheme 18). These observations clearly support the hypothesized formation of a carbocation intermediate during the process.

Interestingly, under iron catalysis, the optically active alcohol (1*RS*,7*R*)-**5f** gave access to the enantiomerically enriched tetrahydropyran (*R*,*R*)-**6f** with no erosion of the enantiomeric excess. In addition, 2,4,6-trisubstituted tetrahydropyrans **6i** and **6j** were prepared in high yields and diastereoselectivities (Scheme 19). These three examples illustrated the great synthetic potential of the developed method.

Scheme 18. Influence of the Geometry of the Double Bond and of the Position of the Leaving Group

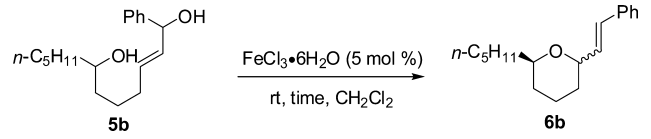


Scheme 19. Synthesis of Optically Active Tetrahydropyrans



The evolution of the diastereomeric ratio during the cyclization of **5b** was monitored by GC/MS analysis, thus highlighting the same epimerization process observed in the case of *N*-nosyl piperidines (Table 2).

Table 2. Monitoring of the *cis*/*trans* Ratio



entry	time (min)	*cis*/*trans*[a]
1	10	55:45
2	30	69:31
3	50	83:17
4	110	97:3
5	240	97:3

[a]Determined by GC/MS.

Consequently, as previously, a mechanism involving an iron-catalyzed reopening of the heterocycle **G** via a zwitterionic intermediate **H** was proposed. This epimerization led to the most stable *cis*-product (Scheme 20).

3.2. Synthesis of Spiroketals

The cyclization conditions were successfully applied to furnish spiroketal **8a** from hydroxyketone **7a** with an excellent diastereoselectivity (Scheme 21).[12a]

This reaction was utilized as a key step for the synthesis of **9**, a precursor of bistramides and analogues. Upon treatment with $FeCl_3$, the functionalized lactol **7b** was diastereoselectively transformed into the bicyclic compound **8b** (59%) thus providing the spiroketal core of bistramides (Scheme 22).[22]

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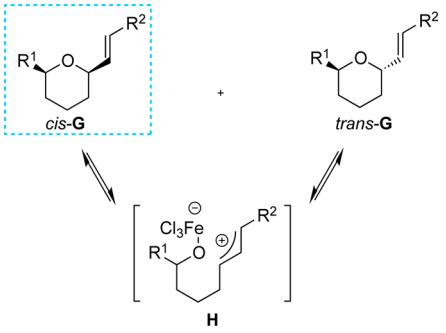
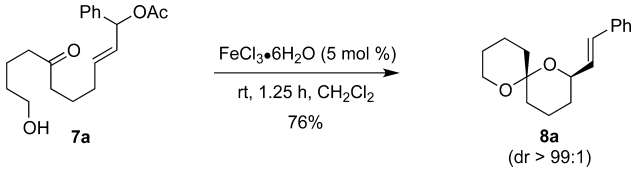
Scheme 20. $FeCl_3$-Induced Epimerization of 2,6-Disubstituted Tetrahydropyrans



Scheme 21. Iron-Catalyzed Synthesis of Spiroketal 8a

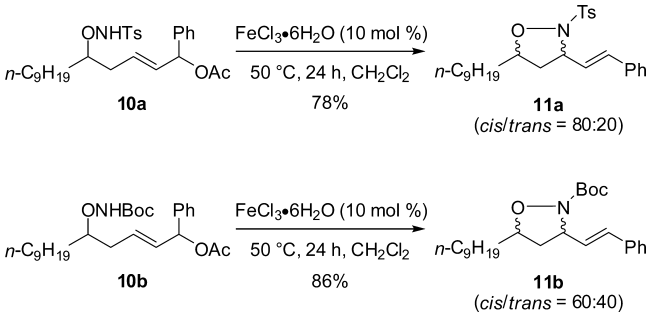


4. IRON-CATALYZED SYNTHESIS OF *N,O*-HETEROCYCLES[14]

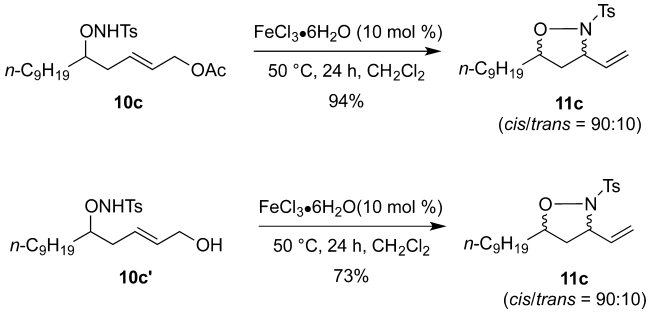
In 2013, we reported that the iron-catalyzed cyclization could be used for the construction of *cis*-isoxazolidines. When the *N*-tosyl hydroxyl amino allylic acetate **10a** was treated with 10 mol % of $FeCl_3 \cdot 6H_2O$ at 50 °C, the corresponding cyclized product **11a** was obtained in a good yield (78%) and with a good diastereomeric ratio of 80:20 in favor of the *cis*-isomer (Scheme 23). Changing the tosyl group for a Boc group slightly improved the yield (86%) but a lower diastereoselectivity was observed (dr = 60:40).

Surprisingly, the absence of any allylic substitutent was not detrimental to the reaction and the isoxazolidine **11c** bearing a terminal olefin was isolated with an excellent yield (94%) and a good diastereomeric ratio (dr = 90:10). This result is in contrast with those observed with other substrates and might be explained by a higher nucleophilicity of the *N*-tosyl hydroxyl amino group. The nature of the leaving group was shown to have an influence on the outcome of the cylization because a lower yield (73%) was observed using allylic alcohol **10c′** instead of allylic acetate **10c** (Scheme 24).

Scheme 23. Formation of Isoxazolidines 11a and 11b



Scheme 24. Influence of the Allylic Substituent and of the Nature of the Leaving Group on the Formation of Isoxazolidines



Several *N*-protecting groups were tolerated under the reaction conditions: similar results were obtained with *N*-tosyl, *N*-nosyl, and *N*-alloc groups (Table 3, entries 1−3). However, the *N*-Cbz isoxazolidine **11f** was isolated in a moderate yield of 63% (Table 3, entry 4), and no conversion of the *N*-Ac and *N*-Boc hydroxylamino allylic acetates was observed (Table 3, entries 5 and 6).

Different alkyl substituents (R^1 = Cy, Me) could be introduced in the α position of the hydroxylamino group providing the corresponding isoxazolidines in good yields (83% in both cases) and satisfying diastereoselectivities (dr = 86:14 and 83:17,

Scheme 22. Synthesis of a Precursor of Bistramides and Analogues

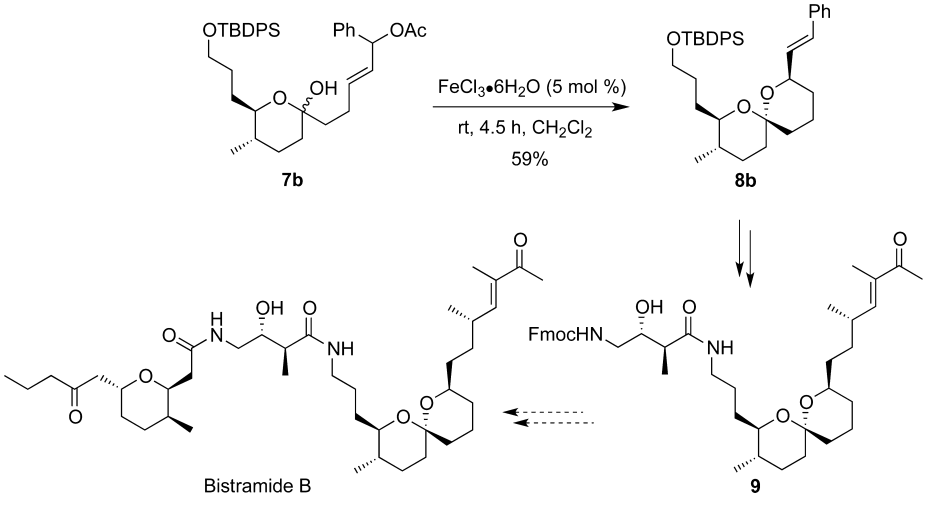


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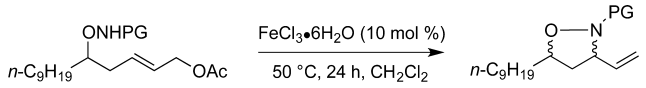
Table 3. Influence of the *N*-Protecting Group



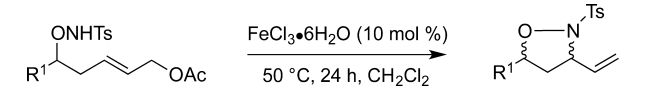
10c-10h **10c-10h**

entry	PG	10	11 (yield, %)	*cis*/*trans*[a]
1	Ts	**10c**	**11c** (94)	90:10
2	Ns	**10d**	**11d** (95)	89:11
3	Alloc	**10e**	**11e** (95)	85:15
4	Cbz	**10f**	**11f** (63)	85:15
5	Ac	**10g**	**11g** (0)	
6	Boc	**10h**	**11h** (0)	

[a]Determined by ^{1}H NMR on the crude mixture.

respectively) (Table 4, entries 1 and 2). The phenyl substituted isoxazolidine **11k** was formed with an excellent yield of 92% and

Table 4. Synthesis of 3,5-Disubstituted Isoxazolidines



10i-10l **11i-11l**

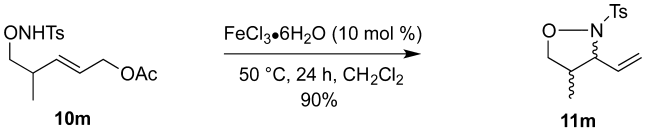
entry	R^1	10	11 (yield, %)	*cis*/*trans* ratio[a]
1	Cy	**10i**	**11i** (83)	86:14
2	Me	**10j**	**11j** (83)	83:17
3	Ph	**10k**	**11k** (92)	86:14
4	CO_2Et	**10l**	**11l** (0)	

[a]Determined by ^{1}H NMR on the crude mixture.

a good diastereoselectivity in favor of the *cis*-isomer (dr = 86:14) (Table 4, entry 3). Disappointingly, the presence of an ester substitutent ($R^1 = CO_2Et$) was not compatible with the reaction conditions since no conversion of the starting material **10l** was observed (Table 4, entry 4).

When the γ-methyl *N*-tosyl hydroxylamino substrate **10m** was treated with $FeCl_3 \cdot 6H_2O$, the expected 3,4-disubstituted isoxazolidine **11m** was formed in good yield (90%) albeit with low diastereoselectivity (dr = 60:40) (Scheme 25).

Scheme 25. Cyclization of γ-Methyl *N*-Tosyl Hydroxylamino Allylic Acetate 10m



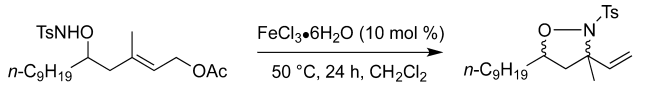
10m **11m** (dr = 60:40)

Interestingly, a quaternary center could be created by cyclization of the allylic acetate **10n** possessing a trisubstituted double bond, which delivered the corresponding isoxazolidines **11n** with an excellent yield (95%) and a moderate diastereomeric ratio (dr = 75:25) (Scheme 26).

A six-membered ring could be formed upon treatment of the *N*-tosyl ε-hydroxylamino allylic acetate **10o**; the reaction proceeded in good yield (85%) but with poor diastereoselectivity (dr = 53:47) (Scheme 27).

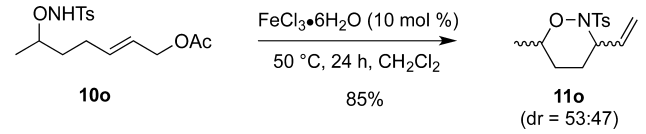
In order to investigate the mechanism of the cyclization, the enantio-enriched acetate (*R*)-**10p** was involved in the iron-catalyzed reaction. The resulting isoxazolidine **11p** was isolated

Scheme 26. Formation of a 3,3,5-Trisubstituted Isoxazolidine



10n **11n** (*cis*/*trans* = 75:25)

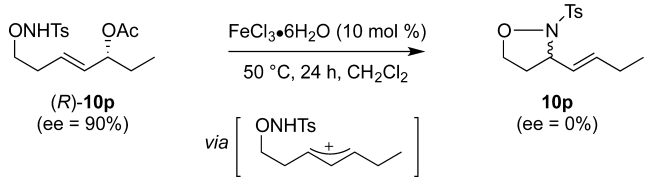
Scheme 27. Synthesis of a Six-Membered Ring



10o **11o** (dr = 53:47)

as a racemic mixture, and the loss of the stereochemical information confirmed the existence of a carbocationic intermediate during the cyclization process (Scheme 28).

Scheme 28. Cyclization of an Enantio-enriched Substrate



(*R*)-**10p** (ee = 90%) **10p** (ee = 0%)

Two separated cases have to be distinguished to account for the observed diastereoselectivity in favor of the *cis*-isoxazolidine. In the presence of a cation stabilizing allylic substituent (R^2 = Ph), an epimerization was observed when a 50:50 mixture of the *cis*/*trans* isoxazolidine **10a** was treated with 10 mol % $FeCl_3 \cdot 6H_2O$, thus suggesting a thermodynamic control. Similarly to what was observed with piperidines and tetrahydropyrans, the more stable *cis*-isomer was formed as the major compound. In contrast, in the absence of any allylic substituent (R^2 = H), no evolution of the diastereomeric ratio was observed upon treatment of isoxazolidine **10c** (*cis*/*trans* = 50:50) even by treatment with 1 equiv of $FeCl_3 \cdot 6H_2O$. Consequently, in this case, the reaction might proceed under kinetic control, and the minimization of the steric interactions in the transition state should be invoked to explain the formation of the major *cis*-isomer (Scheme 29).

The synthetic utility of the unsaturated isoxazolidines obtained by the iron-catalyzed cyclization was demonstrated by the transformation of isoxazolidine **11c** in a variety of valuable compounds. First of all, the N−O bond was reductively cleaved, thus delivering the corresponding amino alcohol **12** in quantitative yield (Scheme 30).

A panel of transformations of the terminal double bond including oxidation, hydroboration, cross-metathesis, and palladium-catalyzed Heck reaction was realized leading to a diversity of coumpounds (Scheme 31).

In addition, the trisubstituted tetrahydropyran **19** was obtained from isoxazolidine **15** using a short synthetic sequence (Scheme 32), illustrating the great synthetic potential of the isoxazolidine derivatives.

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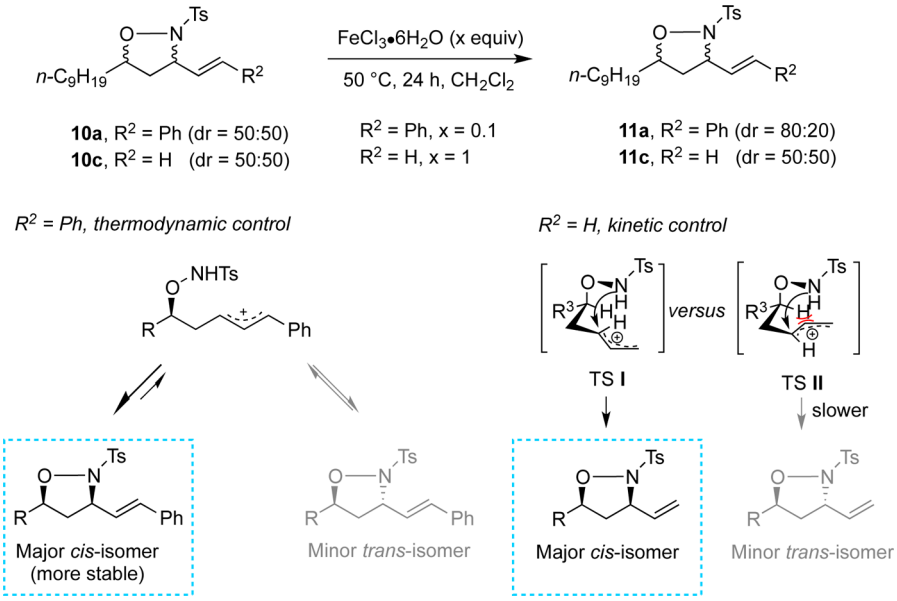
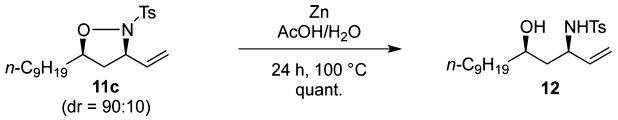
Scheme 29. Mechanistic Considerations



Scheme 30. Reductive Cleavage of the N−O Bond



5. LEWIS ACID-CATALYZED FORMATION OF CYCLIC CARBONATES[15]

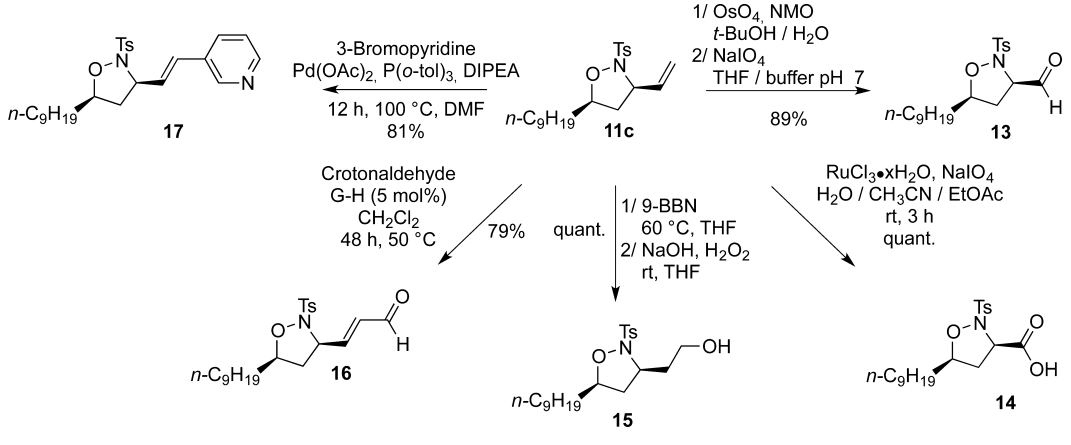
5.1. Six-Membered Cyclic Carbonates

Very recently, we examined the Lewis acid-catalyzed cyclization of the linear *tert*-butyl carbonate **20a** into its corresponding cyclic compound **21a**. When **20a** was treated with $FeCl_3{\cdot}6H_2O$ in CH_2Cl_2, the expected product was obtained in a moderate NMR yield (56%) and moderate diastereoselectivity in favor of the *cis*-isomer (dr = 70:30) (Table 5, entry 1). Pleasingly, the use of acetonitrile instead of dichloromethane increased significantly the yield in **21a**, which was isolated in 74% yield with a dr of 73:27 in favor of the *cis*-isomer (Table 5, entry 2).

The presence of a phenyl allylic substituent (R^2 = Ph) was essential to the cyclization because linear carbonates **20b** and **20c** (R^2 = H and R^2 = C_5H_{11}, respectively) failed to react upon treatment with $FeCl_3{\cdot}6H_2O$ (Table 6, entries 1 and 2). Under iron catalysis, several alkyl-substituted and phenyl-substituted homoallylic *tert*-butyl carbonates were transformed into their corresponding cyclic derivatives in good yields and with moderate diastereoselectivities (Table 6, entries 3−5). The 3,3,5-trisubstituted cyclic carbonate **21g** was obtained from the linear carbonate **20g** albeit with a poor diastereocontrol (Table 6, entry 6).

However, when an ester was present in the starting linear carbonate, a complex mixture of products was obtained upon treatment with $FeCl_3{\cdot}6H_2O$ (Table 7, entry 1). Interestingly, $InCl_3$ revealed to be much more powerful than $FeCl_3{\cdot}6H_2O$ as the cyclic carbonate **21h** was isolated in 54% yield (Table 7, entry 2). As a consequence, the indium complex was preferred for the cyclization of functionalized linear carbonates. In the presence of $InCl_3$, **20i** possessing a phthalimide moiety was cyclized into **21i** in 78% yield and with a 75:25 diastereomeric ratio (Table 7, entry 3). Free alcohols were not compatible, whereas ethers were well tolerated under the reaction conditions (Table 7, entries 4−6). Worthy of note, the presence of halogen atoms was not detrimental to the cyclization (Table 7, entries 5−7).

Scheme 31. Synthesis of Functionalized Isoxazolidines from 11c



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Scheme 32. Synthesis of a Trisubstituted Amido Tetrahydropyran from Isoxazolidines 15

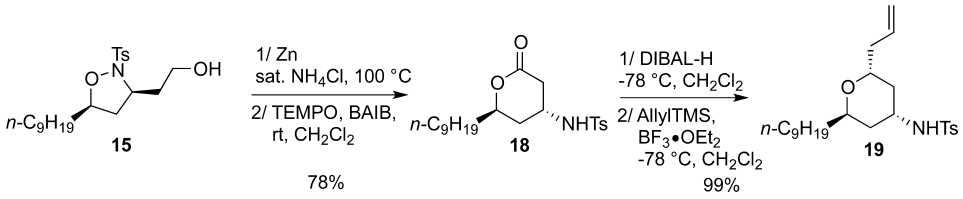
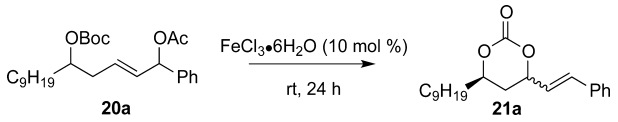


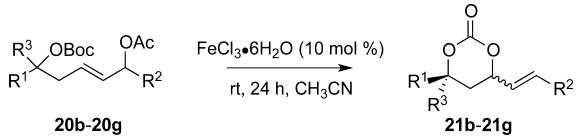
Table 5. Cyclization of Linear *tert*-Butyl Carbonate 20a



entry	solvent	NMR yield,[a] %	*cis*/*trans*[b]
1	CH_2Cl_2	56	70:30
2	CH_3CN	94(74)	73:27

[a]Isolated yields in parentheses. [b]Determined by ^{1}H NMR on the crude mixture.

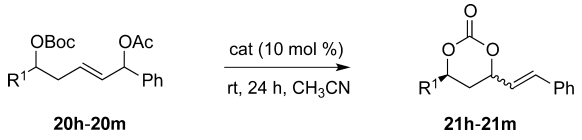
Table 6. Synthesis of Six-Membered Cyclic Carbonates



entry	**20**	R^1	R^2	R^3	**21**, yield (%)	*cis*/*trans*[a]
1	**20b**	Ph	H	H	**21b**, 0	
2	**20c**	Ph	C_5H_{11}	H	**21c**, 0	
3	**20d**	Cy	Ph	H	**21d**, 82	75:25
4	**20e**	Me	Ph	H	**21e**, 89	71:29
5	**20f**	Ph	Ph	H	**21f**, 76	75:25
6	**20g**	C_4H_9	Ph	Me	**21g**, 7	60:40

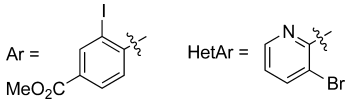
[a]Determined by ^{1}H NMR on the crude mixture.

Table 7. $InCl_3$-Catalyzed Cyclization of Functionalized Linear Carbonates



entry	**20**	R^{1a}	cat.[b]	**21**, yield (%)	*cis*/*trans*[c]
1	**20h**	CO_2Et	[Fe]	**21h**, 0	
2	**20h**	CO_2Et	[In]	**21h**, 54	70:30
3	**20i**	C_3H_6NHPht	[In]	**21i**, 78	75:25
4	**20j**	C_3H_6OH	[In]	**21j**, 0	
5	**20k**	C_3H_6OAr	[In]	**21k**, 79	70:30
6	**20l**	$C_3H_6OHetAr$	[In]	**21l**, 82	73:27
7	**20m**	C_3H_6Br	[In]	**21m**, 79	75:25

[a]

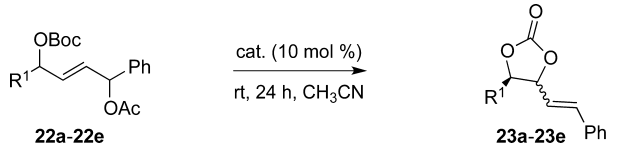


[b][Fe] = $FeCl_3 \cdot 6H_2O$; [In] = $InCl_3$. [c]Determined by ^{1}H NMR on the crude mixture.

5.2. Five-Membered Cyclic Carbonates

The reaction was extended to the formation of five-membered ring cyclic carbonates starting from linear *tert*-butyl carbonates. Iron catalysis was preferred over indium catalysis for the cyclization of alkyl-substituted allylic carbonates **22a** and **22b** (R^1 = C_9H_{19} or Cy), and the corresponding cyclized products **23a** and **23b** were isolated in good to excellent yield albeit with low diastereoselectivity in favor of the *trans*-isomer (Table 8, entries 1 and 2). However, the two diastereomers were separated by flash chromatography on silica gel. The presence of a phenyl substitutent (R^1 = Ph) was detrimental to the cyclization, and a complex mixture of products was obtained regardless the catalytic system (Table 8, entry 3). The indium salt was selected for the cyclization of the more functionalized linear *tert*-butyl carbonates **22d** and **22e** (R^1 = C_3H_6OPMB, $C_3H_6NTsBoc$), which were transformed into the cyclic products **23d** and **23e**, respectively, in good yields (62% and 83%, respectively) but with moderate diastereoselectivity (*cis*/*trans* = 30:70 and 36:64) (Table 8, entries 4 and 5).

Table 8. Synthesis of Five-Membered Cyclic Carbonates



entry	**22**	R^1	cat.[a]	**23**, yield (%)	*cis*/*trans*[b]
1	**22a**	C_9H_{19}	[Fe]	**23a**, 98	37:63
2	**22b**	Cy	[Fe]	**23b**, 81	35:65
3	**22c**	Ph	[Fe], [In]	**23c**, 0	
4	**22d**	C_3H_6OPMB	[In]	**23d**, 62	30:70
5	**22e**	$C_3H_6NTsBoc$	[In]	**23e**, 83	36:64

[a][Fe] = $FeCl_3 \cdot 6H_2O$; [In] = $InCl_3$. [b]Determined by ^{1}H NMR on the crude mixture.

5.3. Mechanistic Considerations

According to our previous studies, the formation of a carbocation during the cyclization was hypothesized. In order to see whether an epimerization was occurring during the reaction, the $InCl_3$-catalyzed cyclization of linear carbonate **20e** was monitored by GC/MS. The absence of any evolution of the diastereomeric ratio suggested a kinetic control; the formation of the major isomer could be explained by the minimization of the steric interactions in the transition state as represented in Scheme 33 for the formation of the major *cis*-six-membered cyclic carbonate.

5.4. Synthetic Potential of the Cyclic Carbonates

Under basic conditions, the synthesized cyclic carbonates **21a** and *cis*-**22b** were easily transformed into their corresponding 1,3- and 1,2-diols, which are ubiquitous motifs in bioactive natural products (Scheme 34).

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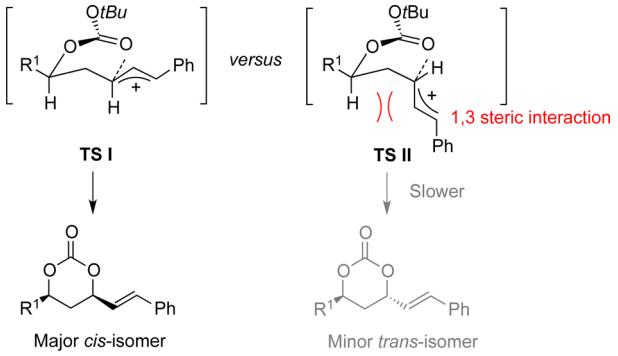
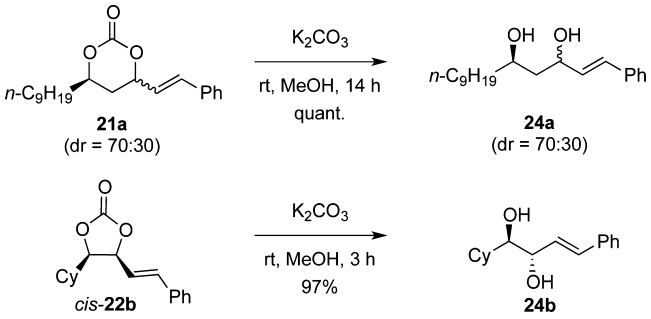
Scheme 33. Hypothesized Kinetic Control during the Cyclization



Scheme 34. Methanolysis of Carbonates 21a and *cis*-22b



The $InCl_3$-cyclization was used as the key step in a short synthesis of (3*S*,5*S*)-alpinikatin, a natural product belonging to the diarylheptanoid recently extracted from the seeds of *Alpinia katsumadai*.[23] The methyl 3-(4-hydroxyphenyl)propionate was protected as a TBS ether and a reduction of the ester moiety provided the corresponding aldehyde, which was submitted to an enantioselective allyltitanation using the (*S*,*S*)-**Ti-I** reagent.[24] The resulting enantio-enriched homoallylic alcohol **25** was involved in a cross-metathesis with 1-phenylallyl acetate,[25] and the resulting alcohol **26** was transformed into the *tert*-butyl carbonate **27**. In the presence of $InCl_3$, the linear *tert*-butyl carbonate **27** delivered the cyclic product (dr = 73:27), which was immediately converted into (3*S*,5*S*)-alpinikatin through methanolysis (Scheme 35).

6. CONCLUSION

Over the past five years, we have developed a Lewis acid-catalyzed cyclization allowing access to a large variety of heterocycles such as piperidines, pyrrolidines, tetrahydropyrans, spiroketals, isoxazolidines, and cyclic carbonates. In most cases, $FeCl_3{\cdot}6H_2O$ proved to be a powerful catalyst, thus providing cheap, low toxicity, and environmentally friendly reactions. The reactions generally proceed in high yields and with excellent to moderate diastereoselectivities, which is an attractive alternative to Pd- or Au-catalyzed cyclizations. The use of Lewis acid-catalyzed heterocyclizations as key steps in the preparation of highly functionalized compounds such as natural products demonstrates their great synthetic potential.

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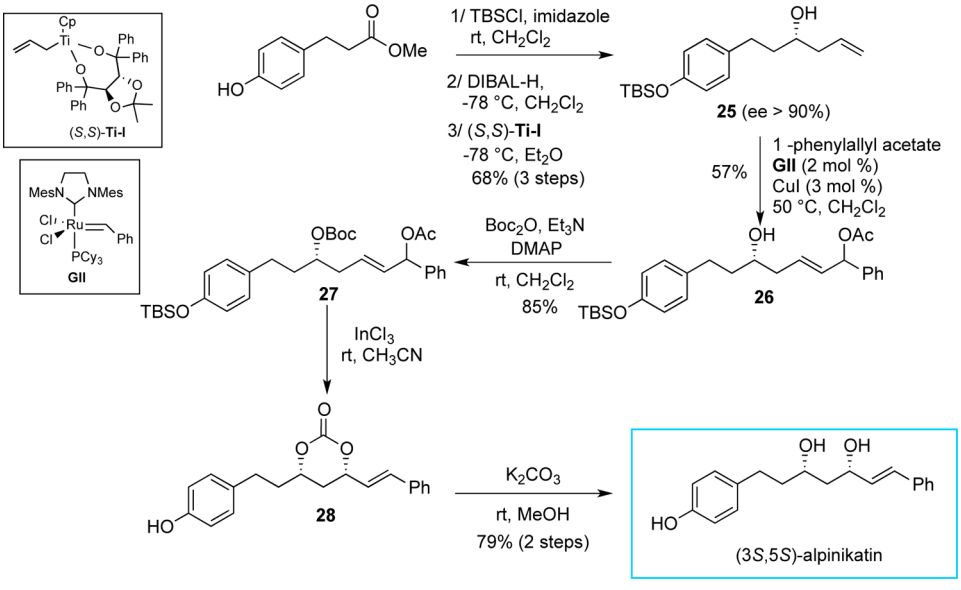
Notes

The authors declare no competing financial interest.

Biographies

Johan Cornil was born in Tremblay-lès-Gonesse, France in 1987. He received his engineer's diploma from Chimie ParisTech in 2011 and then prepared his Ph.D. at ESPCI ParisTech under the supervision of Dr. Sébastien Reymond, Dr. Amandine Guérinot, and Prof. Janine Cossy in the field of metal catalysis and synthesis of natural products. He obtained his Ph.D. from the University Pierre et Marie Curie in 2014.

Scheme 35. Total Synthesis of (3*S*,5*S*)-Alpinikatin



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Laurine Gonnard was born in 1991 in Mont-Saint-Aignan, France. She received her engineer's diploma from ESPCI ParisTech in 2014 and then joined the organic chemistry laboratory at ESPCI ParisTech to prepare her Ph.D. under the supervision of Dr. Amandine Guérinot and Prof. Janine Cossy.

Charlélie Bensoussan was born in Martigues, France, in 1986. He studied chemistry at ESPCI ParisTech, where he received his engineer's degree in 2009. He then completed his Ph.D. in organic chemistry in 2012, under the supervision of Dr. Sébastien Reymond and Prof. Janine Cossy, working on the synthesis of amphidinol 3 and iron-catalyzed reactions. He is now a Strategy and Marketing Senior Consultant at Vertone, Paris.

Anna Serra-Muns was born in Vic, Spain. She received her B.Sc. and Ph.D. degree in Chemistry from the Autonomous University of Barcelona (UAB) in 2003 and 2008, respectively. After one-year as a postdoctoral fellow at the Ecole Normale Supérieure (ENS) in Paris, she joined the ESPCI ParisTech as a postdoctoral fellow with Prof. Janine Cossy. She is currently working at OPKO HEALTH SPAIN as Export Manager of drugs, diagnostic kits, food supplements, and medical devices.

Christian Gnamm was born in Heidelberg, Germany, in 1979. He received his diploma in chemistry from the University of Heidelberg in 2005. During his Ph.D. thesis, he worked in the field of iridium-catalyzed allylic substitutions with Prof. Günter Helmchen (Heidelberg) and on iron-catalyzed allylic cyclizations with Prof. Janine Cossy at ESPCI ParisTech. He obtained his Ph.D. from the University of Heidelberg in 2009 and then joined Syngenta in Switzerland as a postdoctoral fellow. Since 2010, he has been working as medicinal chemist in drug discovery at Boehringer Ingelheim in Biberach, Germany.

Claude Commandeur was born in 1976 in St Martin d'Hères, France. He received his Ph.D. degree in organic chemistry under the supervision of Prof. Max Malacria in 2003 from Université Pierre et Marie Curie (Paris 6). After two years as a postdoctoral fellow at SUNY Stony Brook (New York, U.S.A.) under the supervision of Prof. Iwao Ojima, he joined IECB (Pessac, France) as postdoctoral fellow (ARC) in the group of Dr. Michel Laguerre. From 2007 to 2009, he worked as postdoctoral fellow in the group of Prof. Léon Ghosez in collaboration with Syngenta (Switzerland). He moved to Paris, first at Institut Curie under the supervision of Dr. Jean-Claude Florent then he joined the group of Prof. Janine Cossy for a postdoctoral stay in collaboration with Laboratoires Pierre Fabre. Since 2013, he has been team leader in the R&D Department at Selvita S.A. in Krakow, Poland.

Malgorzata Commandeur was born in Radom, Poland. She received her Ph.D. degree in organic chemistry under the supervision of Prof. Janusz Jurczak in 2003 from Warsaw University (Poland). After two years as a postdoctoral fellow at M.D. Anderson Cancer Center (Houston, U.S.A.), she joined the group of Prof. Léon Ghosez for a postdoctoral stay in collaboration with Syngenta (Switzerland) from 2006 to 2009. She then moved to ESPCI ParisTech with Prof. Janine Cossy as a postdoctoral fellow where she was involved in the synthesis of bistramides. Since 2013, she has been team leader in the Contract Chemistry Department at Selvita S.A. in Krakow, Poland.

Sébastien Reymond was born in Valence, France, in 1975. He received his engineer's diploma in 1999 from ENSSPICAM, now Ecole Centrale de Marseille, and his Ph.D. in 2003 from the University of Aix-Marseille III in the group of Prof. Gérard Buono. After a one-year postdoctoral stay with Prof. Jean-Pierre Genêt at ENSCP in Paris, he was appointed Associate Professor in 2004 at ESPCI ParisTech in the group of Prof. Janine Cossy. His research interests include the development of ecofriendly synthetic organic methods, iron catalysis, and the synthesis of biologically active compounds.

Amandine Guérinot was born in 1983 in Troyes, France. She received her engineer's diploma from ESPCI ParisTech in 2007 and her Ph.D. in 2010 from the University Pierre et Marie Curie under the supervision of Dr. Sébastien Reymond and Prof. Janine Cossy. She joined the group of Prof. Sylvain Canesi at UQAM, Montreal, as a postdoctoral associate and then moved to ICMMO, Orsay, France, for a one-year postdoctoral stay with Prof. Vincent Gandon. After a six months postdoctoral fellowship with Dr. Laurent Micouin (Paris Descartes University), she was appointed Associate Professor in 2013 at ESPCI ParisTech in the group of Prof. Janine Cossy. Her research interests include organometallic cross-couplings, iron catalysis, and synthesis of biologically active compounds.

Janine Cossy's early career was spent in Reims, where she did her undergraduate and graduate studies at the University of Champagne-Ardenne, working on photochemistry under the supervision of Prof. Jean Pierre Pète. After a postdoctoral stay with Prof. Barry Trost, for two years at the University of Wisconsin (USA), she returned to Reims where she became, in 1990, Director of Research of CNRS. In the same year, she moved to Paris and since 1990, she has been Professor of Organic Chemistry at the ESPCI ParisTech. Since 2005, she has been *Organic Letters* Associate Editor. Janine Cossy's research interests focus on the synthesis of natural products and biologically active molecules (antibiotics, antitumoral and anti-inflammatory agents and compounds active on the central nervous system). The synthetic methods that she develops and applies include radical reactions, photochemistry, thermal reactions, organometallic reactions, catalysis, ring expansions, opening of strained rings, methods for the synthesis of heterocyclic compounds, and stereoselective reactions. Her research efforts have resulted in more than 425 publications and 15 patents. Among the awards, she received the CNRS Bronze Medal (1987), the CNRS Silver Medal (1996), UK Royal Society Rosalind Franklin International Lecturership awarded to internationally recognized women scientists (UK) (2005), and Le Bel Award from the French Chemical Society (France) (2009), and she was nominated Chevalier de la Légion d'Honneur in 2013.

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