Enantiodivergent Synthesis of (+)- and (-)-Pyrrolidine 197B. Synthesis of *trans*-2,5-Disubstituted Pyrrolidines via Intramolecular Hydroamination.

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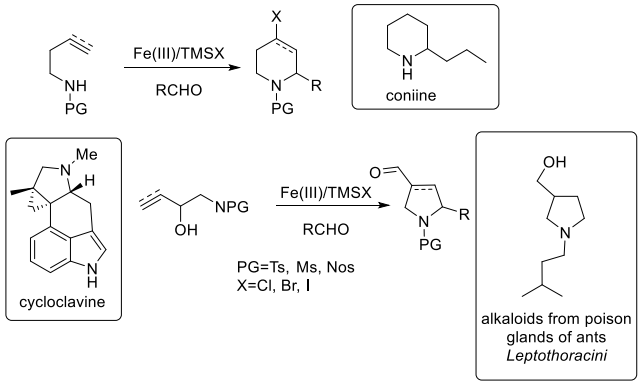
Abstract: A highly efficient diastereoselective iron(III)-catalyzed intramolecular hydroamination/cyclization reaction involving α-substituted amino alkenes is described. Thus, enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-substituted proline derivatives are synthesized by means of the combination of enantiopure starting materials, easily available from *L*-α-amino acids, with sustainable metal catalysts such as iron(III) salts. The scope of this methodology is highlighted in an enantiodivergent approach to the synthesis of both (+)- and (-)-pyrrolidine 197B alkaloids from *L*-glutamic acid. In addition, a computational study was also carried out to gain insight into the complete diastereoselectivity of the transformation.

Introduction

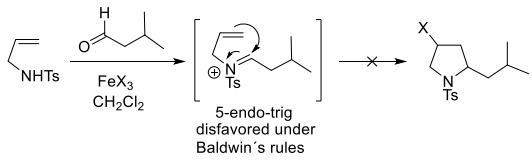
Five-membered azacycles are common structural units present and widespread in the fields of organic and medicinal chemistry. Thus, they can be found in a good number of natural products containing the parent pyrrolidine ring, organocatalysts having optically active prolines or derivatives, and drugs.[1-3]

Over the last decade, our research group has been involved in the synthesis of azacycles of several sizes using the Prins cyclization and iron(III) salts as sustainable catalysts.[4] We have developed new methodologies to generate substituted piperidines and tetrahydropyridines which were applied to the synthesis of different natural products such as coniine (Scheme 1).[5] On the other hand, the synthesis of 3,5-disusbstituted pyrrolidines and pyrroles was accomplished through the aza-Cope Mannich tandem cyclization, and applied to the synthesis of the male-attracting pheromones from the poison glands of ants *Leptothoracini*.[6] More recently, Cao et al. have used this aza-Cope Mannich procedure as the key reaction in the formal synthesis of cycloclavine and the construction of the ACDE ring system of Daphenylline (Scheme 1).[7]



Scheme 1. Synthesis of five- and six membered rings azacycles development in our group, and their application to the natural product synthesis.

As a continuation of our previous work, we have now focused on the synthesis of *trans*-2,5-disubstituted pyrrolidines and their application towards the synthesis of natural products. However, the direct access to these type of azacyles, through an aza-Prins cyclization does not occur, which agrees with a disfavored 5-endo-trig cyclization according to the Baldwin's rules (Scheme 2).[8,9]



Scheme 2. The direct aza-Prins cyclization in the synthesis of substituted pyrrolidines.

Therefore, the development of new methodologies allowing both the efficient and stereocontrolled access to these nitrogen heterocycles represents a target as well as a challenge for synthetic organic chemists. Among these methodologies, the intramolecular hydroamination reaction (IHR) has become nowadays one of the most powerful tool towards the synthesis of

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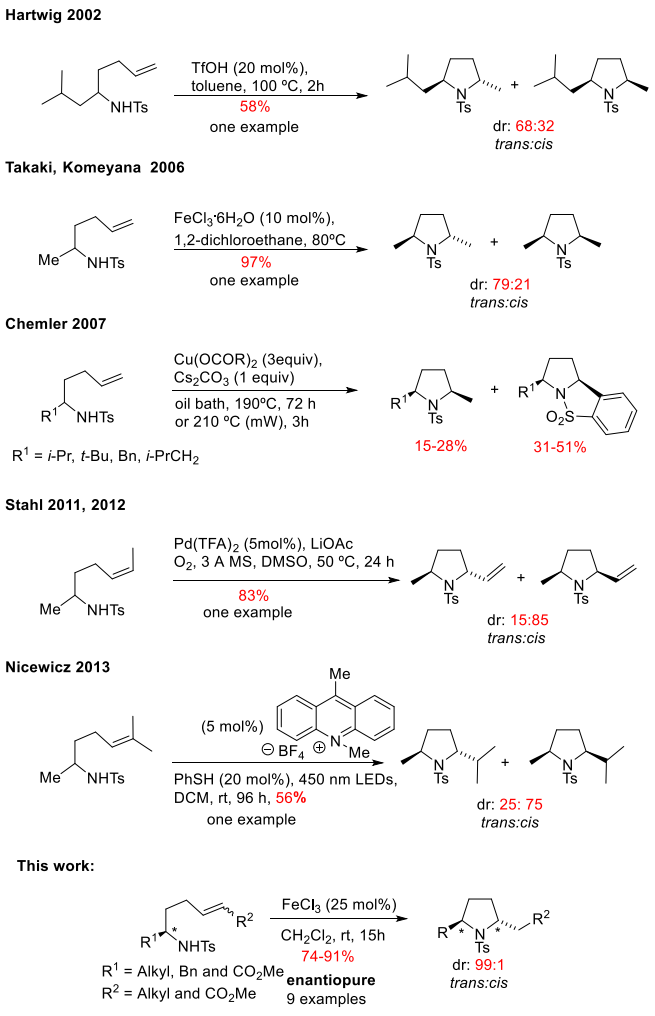
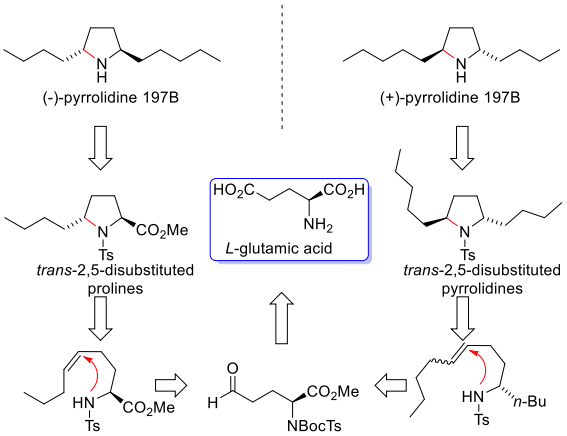
azacycles.[10] This process involves the direct addition of nitrogen and hydrogen atoms to carbon-carbon multiple bonds with atom economy. Moreover, it is well-known that the hydroamination of alkenes is comparatively more difficult than that to alkynes because of the lower reactivity and electronic density of the C=C double bond. Although the enantioselective olefin hydroamination constitutes potentially a powerful and efficient approach, the reported procedures so far are typically based on using rare and expensive transition-metals and ligands.[10,11,37e] It would therefore be desirable to overcome this shortcoming by using a sustainable strategy that would combine an inexpensive and bio-relevant metal with accessible and abundant enantiopure compounds, such as iron and amino acids, respectively.[12]



Scheme 3. Previous strategies and our work to access *trans*-2,5-disubstituted pyrrolidines.

To our knowledge, despite the enormous interest on iron catalysis and hydroamination reactions,[13] there exist only a few examples on iron-catalyzed intramolecular hydroamination reactions involving either protected or unprotected amines and unactivated alkenes.[14] In these cases, the process involves primary aliphatic amines and leads to the racemic synthesis of 2-substituted pyrrolidines.[15] Therefore, a complete diastereoselective iron-catalyzed hydroamination/cyclization reaction involving α-substituted amino alkenes in an enantiomeric context is still missing (Scheme 3).[14a,16]

Herein, we shall describe the first diastereoselective synthesis of enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-substituted proline derivatives by means of the combination of iron(III) salts, as a sustainable metal catalyst, with enantiopure starting materials such as amino acids. Then, we hypothesized that within this methodology in hand, it could be possible to exploit *L*-glutamic acid in an enantiodivergent manner that would allow the access to both (+)- and (–)-pyrrolidine 197B (Scheme 4), alkaloids with known hemolytic and antibiotic activities.[17]

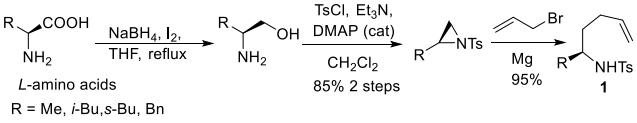


Scheme 4. Enantiodivergent strategy for the preparation of (+)- and (–)-pyrrolidine 197B.

Results and Discussion

Diasteroselective synthesis of *trans*-2,5-disubstituted pyrrolidines

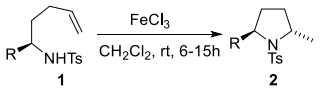
With the idea to find a fully diasteroselective synthesis of *trans*-2,5-disubstituted pyrrolidines, as a base of the enantiodivergent synthesis, we initiated this study by exploring the IHR involving enantiopure α-substituted aliphatic sulfonylamines **1** and iron(III)-chloride as catalyst in a sustainable context (Table 1).[18] The α-substituents in **1** come directly from the corresponding initial α–amino acids used in the preparation of the substrate.[19] This consists on the initial reduction of the amino acid to β-amino alcohol using $NaBH_4$ and iodine, followed by formation of the corresponding *N*-tosyl aziridines by sequential *O*-tosylation and intramolecular cyclization.[18a] Finally, the regioselective opening of the *N*-tosyl aziridine ring, by treatment with allylmagnesium bromide, afforded the *N*-tosyl *bis*-homoallyl amines **1** with very good yields (Scheme 5).



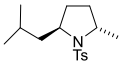
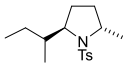
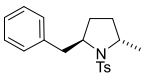
Scheme 5. Synthesis of α-alkyl-*bis*-homoallyl tosylamines **1**.

Thus, we began our study by treating (*S*)-*N*-(hex-5-en-2-yl)-tosylsulfonamide **1** (R = Me) with equimolecular amounts of $FeCl_3$ (100 mol%) in dry dichloromethane at room temperature for 6h. Whitin these reaction conditions, (2*S*, 5*S*)-2,5-dimethyl-1-tosylpyrrolidine **2** was isolated in quantitative yield (Table 1, entry 1). Cyclization of this α-methyl substituted tosylaminopentene **1** proceeded, therefore, with excellent *trans* diastereoselectivity. Indeed, pyrrolidine **2** was isolated exclusively and no traces of the corresponding *cis*-pyrrolidine isomer were detected in the reaction crudes.[20] The intramolecular hydroamination reaction also works well with different α-aliphatic substituents leading to similar reaction yields (Table 1, entries 2 and 3). Replacement of the α-substituent by a benzyl group, coming from phenylalanine as enantiopure starting source, has no significant effect on the reaction yield either (84%, Table 1, entry 4).[21] Interestingly, a decrease of the amount of $FeCl_3$ increased the reaction time and provoked only a slight decrease in the reaction yields, which is more evident when using 10 mol% of this iron(III)-halide (see Table 1).[22] This intramolecular hydroamination procedures constitutes therefore a stereoselective cyclization reaction which exclusively affords the corresponding *trans*-pyrrolidine derivative regardless of the type of α-substituents present in the initial sulfonylamino alkene and/or reaction conditions.

Table 1. Intramolecular hydroamination of α-substituted sulfonyl amine alkenes using iron(III) chloride.[a]



1 2

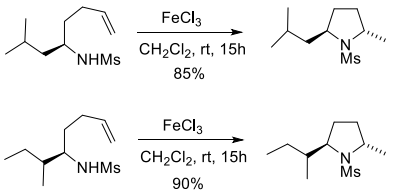
Entry	Product **2**	[%][b] $FeCl_3$ (100 mol%)	[%][b] $FeCl_3$ (50 mol%)	[%][b] $FeCl_3$ (25 mol%)	[%][b] $FeCl_3$ (10 mol%)
1		>99	>99	91	90
2		>99	97	74	50
3		96	90	82	66
4		84	81	75	61

[a] reactions conditions: **1** (1.0 mmol), $FeCl_3$, dry CH_2Cl_2 (0.1 M), rt, 6-15 h, open to air. [b] Isolated yields of products after purification by silica gel column chromatography. Ts = *p*-toluensulfonyl.

Theoretical calculations on Iron(III)-catalyzed alkene-intramolecular hydroamination

At this point, it is important to take into account that two different reaction mechanisms can be envisaged for this IHR, namely a) a simple acid-catalyzed Markovnikov hydroamination through a direct or indirect interaction with the alkene functionality,[16a] or b) direct participation of the transition metal moiety in the cyclization, which therefore controls the diastereoselevity of the process. In our reactions, anhydrous $FeCl_3$ is used at room temperature and formation of HCl was not expected. Furthermore, when the reactions are carried out in the presence of trimethylsilylchloride (1 equiv.) that could decompose generating HCl, no cyclization was observed. This fact nicely agrees with the observations by Takaki and Komeyana (Scheme 3), which confirm that a simple acid-catalyzed pathway does not contribute to the reaction. Indeed, these authors used $FeCl_3{\cdot}H_2O$ at 80º C that can produce Fe_2O_3 and HCl. In addition, HCl (30 mol%) and others catalysts such as *p*-toluensulfonic acid or/and phenylacetic acid were also tested finding that no reaction took place under similar conditions.[14a] Therefore, the acid-catalyzed mechanism can be safely ruled out.

On the other hand, and according with the precedents highlighted in Scheme 3, the presence of the tosyl group is not translated into a full diastereoselectivity process. Hartwig, and Takaki and Komeyana obtained a low diastereoselectivity favoring the *trans*-pyrrolidines by using triflic acid and $FeCl_3{\cdot}H_2O$ respectively.[14a,16a] At variance, Chemler, Stahl and Nicewicz obtained the *cis*-pyrrolidines as major isomer using others catalysts based on cooper, palladium or organic iminiun salt.[16c-d]



Scheme 6. Synthesis of *trans*-2,5-disubstituted *N*-mesyl pyrrolidines.

According to these results, we decided to decrease the size of the *N*-sulfonyl group and study its influence on the course of the IHR catalyzed by iron(III)chloride. The size of this group was reduced by using a *N*-mesyl group instead of a *N*-tosyl group (methanesulfonyl instead *p*-toluensulfonyl, Scheme 6). We synthesized the unsaturated analogues *N*-mesyl derivatives of **1** following the same synthetic sequence described above (see scheme 5). The treatment of the *iso*-butyl- and *sec*-butyl-*bis*-homoallylmesyl amine with $FeCl_3$ (1 equiv.) leads to the corresponding *trans N*-mesyl pyrrolidines with very good yields, showing that the volume of the substituent attached to the sulfonyl group has not direct influence on the diastereoselectivity of IHR (Scheme 6).

Finally, the diastereoselectity of the reaction was not affected upon variation of the reaction temperature (refluxing or cooling) which only modifies the reaction time. Despite that, it seems that the tosyl or mesyl groups are not mere spectators in the process as it is confirmed by means of theoretical calculations (see below).

Density Functional Theory (DFT) calculations[23] were carried out to gain more insight into the complete diastereoselectivity of the above described $FeCl_3$-catalyzed hydroamination reaction. To this end, we computed the reaction profile involving the tosylamino pentene **1** (R = Me) in the presence of $FeCl_3$ as catalyst. The results are shown in Figure 1, which gathers the corresponding relative electronic (ΔE) in CH_2Cl_2 solution (PCM(CH_2Cl_2)-M06/def2-TZVP//M06/def2-SVP level).

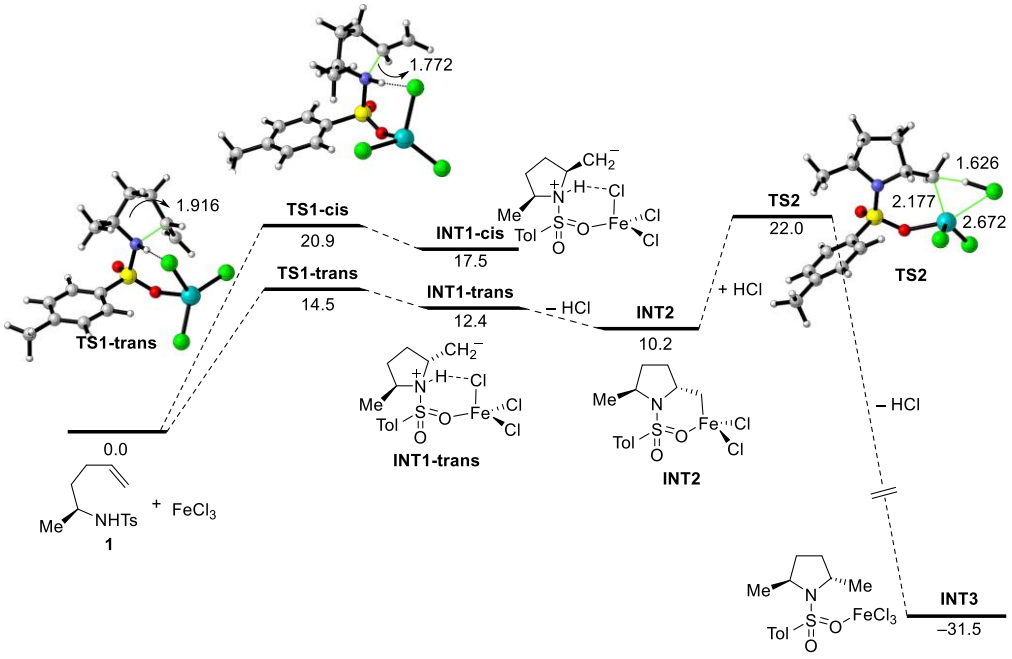


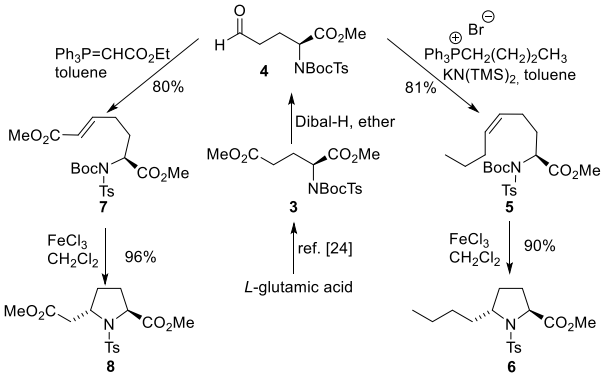
Figure 1. Computed reaction profiles for the reaction of tosylamino pentene **1** in the presence of $FeCl_3$. Relative electronic (ΔE, ZPVE included) and bond distances are given in kcal/mol and angstroms, respectively. All data have computed at the PCM(CH_2Cl_2)-M06/def2-TZVP//M06/def2-SVP level.

From the data in Figure 1, it becomes clear that the intramolecular cyclization reaction exclusively leads to the formation of the *trans*-azacyclic intermediate **INT1-*trans*** through the transition state **TS1-*trans*** ($\Delta E^{\neq}$ = 14.5 kcal/mol) in an endothermic reaction (ΔE_R = 12.4 kcal/mol). The complete diastereoselectivity of the process takes place under both kinetic and thermodynamic control, in view of the considerably higher activation energy ($\Delta E^{\neq}$ = 20.9 kcal/mol, via **TS1-*cis***) and endothermicity ($\Delta\Delta E_R$ = 5.1 kcal/mol) associated with the formation of the alternative **INT1-*cis*** intermediate. Please note that our calculations reveal the active effect of the *N*-tosyl group in the process. As shown in the optimized geometries of the transition states depicted in Figure 1, the oxygen atom of the sulfonyl group is strongly coordinated to the $FeCl_3$ catalyst thus facilitating the cyclization reaction. This interaction is present along the entire reaction coordinate. In addition, zwitterionic intermediate **INT1-*trans*** (and its *cis*-counterpart) is stabilized by an intramolecular NH···ClFe hydrogen bond (computed bond distance of 1.885 Å) which weakens the corresponding Fe**–**Cl bond (the associated computed Wiberg Bond Index for this Fe–Cl bond is 0.40, which is much lower than those computed for the adjacent Fe–Cl bonds, 0.63 and 0.65, respectively). As a result, a molecule of HCl can be easily released with concomitant formation of a new Fe–CH_2 bond in an exothermic process leading to **INT2** (ΔE_R = –2.2 kcal/mol). The last step of the process involves the protonolysis of the Fe–CH_2 bond in **INT2** promoted by HCl through the transition state **TS2** ($\Delta E^{\neq}$ = 11.8 kcal/mol), a saddle point associated with the Fe–C bond rupture/C–H bond formation). This transformation produces the $FeCl_3$-coordinated *trans*-pyrrolidine **INT3** in a highly exothermic reaction (ΔE_R = –41.7 kcal/mol). The great exothermicity of this step compensates the endothermicity computed for the initial intramolecular cyclization reaction and drives the entire transformation forward.

Finally, the reaction ends up with the decoordination of $FeCl_3$ in **INT3**, which would enter in a new catalytic cycle, releasing the experimentally observed *trans*-*N*-tosylpyrrolidine **2**.

Diasteroselective synthesis of *trans*-5-substituted proline derivatives

Next, we focused on the synthesis of enantiopure *trans*-5-substituted proline derivatives, exploring the compatibility of $FeCl_3$ with tosylamino alkenes having an ester group as α-substituent and an internal double bond (Scheme 7).



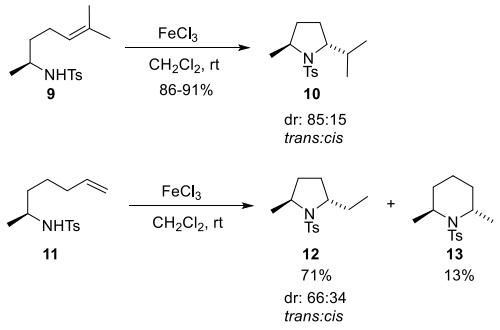
Scheme 7. Diastereoselective intramolecular hydroamination. Synthesis of *trans*-5-substituted proline derivatives

The Wittig olefination of aldehyde **4** with either unstabilized or stabilized ylides provided the desired unsaturated tosylamines **5** and **7**, respectively (Scheme 7). Subsequent treatment of these tosylamino alkenes with $FeCl_3$ permitted us to remove the *N*-Boc group with concomitant IHR in a single reaction step with excellent reaction yields.[25] In both cases, the enantiopure *trans*-5-

substituted proline derivatives were obtained regardless of the stereochemistry of the initial double bond (Scheme 7). The access to these *trans*-5-substituted prolines could be achieved in a few steps by means of *N*-detosylation and hydrolysis of the ester functionality. [26]

This methodology opens a new way to synthesize *trans*-5-substituted prolines with potential applications in organocatalysis and medicinal chemistry.[27] In six reaction steps, *trans*-5-alkyl proline derivatives such as **6** can be produced by modulating the size of the aliphatic chain using the corresponding phosphonium salt (Scheme 7). On the other hand, the synthesis of proline derivatives such as **8** having an additional ester in a distal position, allows further modifications as well. Furthermore, our method complemented the known syntheses of 5-substituted prolines based, among others, on Streker-type reaction,[28] reductive amination,[29] 5-endo-dig cyclization,[30] addition of Grignard reagents to oxazolidines,[31] β-decarboxylation-*N*-cyclization,[32] carbenoid chemistry,[33] hydroboration-oxidation reaction,[34] oxidative cleavage of bicyclic skeleton,[35] and radical cyclization.[36]

The scope of our methodology was checked next. To this end, we used trisubstituted alkene **9** and tosylamino alkene **11** which may lead to the corresponding piperidine derivative (Scheme 8). According to optimized conditions (Table 1), we treated both compounds with 25 mol% and 100 mol% of $FeCl_3$.

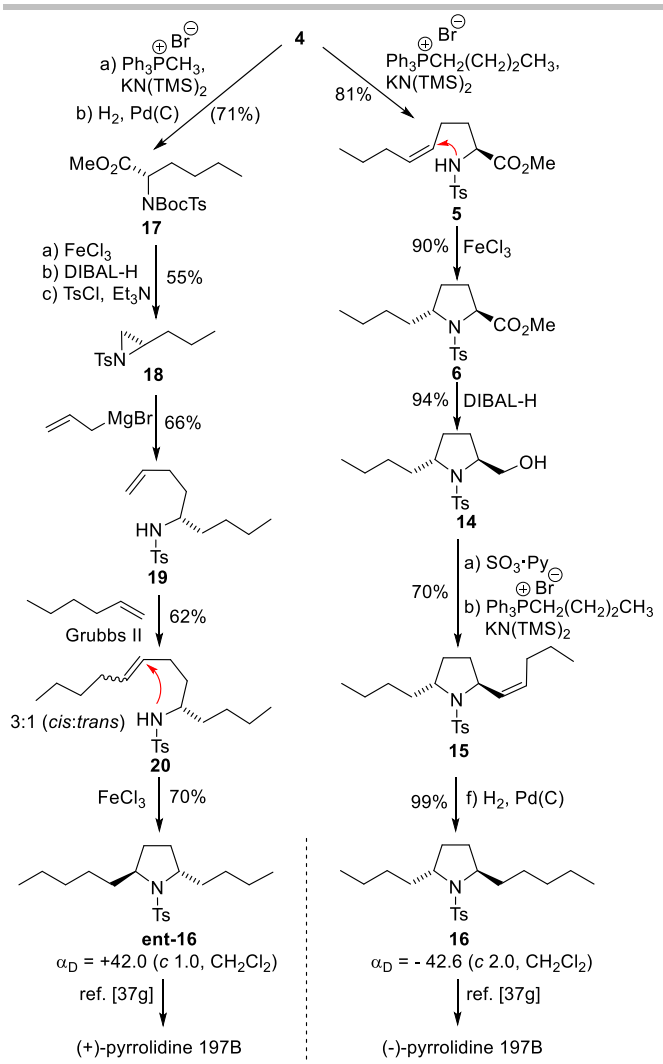


Scheme 8. IHR of tosylamino alkenes with trisubstituted double bond and bearing a longer aliphatic-chain.

As clearly seen in Scheme 8, the substitution of the double bond does not affect the IHR and the *trans*-2-isopropyl-5-methyl-1-tosylpyrrolidine (**10**) could be obtained in very good yield (Scheme 8). The reaction works really well either under catalytic or stoichiometric conditions (86% for 25 mol% and 91% for 100 mol% of $FeCl_3$). In the approach to 2,6-disubstituted piperidine, the treatment of *N*-tosyl-2-amino-6-heptene (**11**) with $FeCl_3$ leads to a mixture of five- and six-membered ring respectively, being the 2,5-*trans* pyrrolidine the preferred reaction product. This behavior is similar to that observed by Takaki, Komeyana et al. and might be caused by an isomerization of the double bond during the process.[14a] In this particular case, no reaction was observed under catalytic conditions (25 mol% of $FeCl_3$).

With this methodology in hand, that makes it possible the synthesis of enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-substituted proline derivatives, we decided to synthesize the alkaloids (+)- and (–)-pyrrolidine 197B in an enantiodivergent strategy.[37] As depicted in the working plan (Scheme 4), we envisaged *L*-glutamic acid as the key enantiopure starting material. The synthesis of (-)-pyrrolidine 197B was conducted through the *trans*-5-substituted proline pathway, in which the α-substituent ester group was modified after the intramolecular hydroamination/cyclization reaction. The homologation of the aldehyde **4** through a Wittig olefination and *N*-Boc deprotection/IHR promoted by iron(III) chloride sequence led to the *trans*-proline derivative **6** previously described above (Scheme 7). Reduction of the ester group was performed with DIBAL-H to provide the primary alcohol **14**, from which the aliphatic chain is then installed (Scheme 9). This linear aliphatic chain was generated in a three steps reaction sequence involving Parikh-Doering oxidation, Wittig reaction with unstabilized ylide and final hydrogenation of the *cis*-olefin **15**. The resulting (2*R*, 5*R*)-2-butyl-5-pentyl-1-tosylpyrrolidine **16** constitutes the Davis intermediate to one step away of the (–)-pyrrolidine 197B synthesis.[37g]

In the case of (+)-enantiomer synthesis, the ester at the α-position was modified before IHR in the *trans*-2,5 pyrrolidine pathway. Again, we started with a Wittig reaction over the aldehyde **4** that permits, after the corresponding hydrogenation reaction, the installation of one of the side chains of (+)-pyrrolidine 197B. This pathway is based on the formation of the tosylaziridine **18**, which was accomplished in three steps from ester **17**. Iron(III)-promoted *N*-Boc deprotection generated the corresponding *N*-tosyl α-amino ester,[25] which was subsequently reduced to the corresponding *N*-tosyl β-amino alcohol. The synthesis of *N*-tosyl aziridine **18** (*L*-norleucine derivative) was carried out in a single step that involves a sequential *O*-tosylation and a final intramolecular cyclization.[18a] The regioselective opening of the *N*-tosyl aziridine ring, by treatment with allylmagnesium bromide, afforded the desired *N*-tosyl *bis*-homoallyl amine **19**. Next and prior the final IHR, the second aliphatic side chain was installed through an alkene-metathesis reaction. Finally, the *trans N*-tosyl pyrrolidine **ent-16** was obtained by the iron(III) chloride-promoted IHR with an excellent reaction yield. Clearly, it is again confirmed that the final stereochemistry of **ent-16** does not depend on the stereochemistry of the double bond in compound **20**. Compared to previous syntheses, our enantiodivergent approach to (+)- and (-)-pyrrolidine 197B is much shorter than the only enantiodivergent approach reported by Machinaga and Kibayashi. Our syntheses required 9 and 7 steps, respectively. In contrast, their syntheses required 16 steps starting from C2-symmetric diepoxides derived from *D*-mannitol.[37a,37b] Concerning the synthesis of (+)-pyrrolidine 197B, to the best of our knowledge, our approach with 9 steps is at the same level to the best syntheses published, namely Takahata and Momose (10 steps),[37c] Mandille (8 steps)[37d] and Marks (10 steps) approaches.[37e] With respect to the preparation of (-)-pyrrolidine 197B, our approach is the shortest synthesis reported to date together with Davis proposal (i.e. Lhommet, 8 steps, and Davis, 7 steps).[37f, 37g]



Scheme 9. Formal synthesis of (+)- and (-)-pyrrolidine 197B.

Conclusions

In summary, we have established a novel method to obtain enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-substituted proline derivatives by means of the combination of iron(III) salts, as a sustainable metal catalyst, with enantiopure α-amino acids. A complete diastereoselective iron-catalyzed intramolecular hydroamination/cyclization reaction involving α-substituted amino alkenes in an enantiomeric context is therefore described. According to our DFT calculations, the complete diastereoselectivity of the process takes place under both kinetic and thermodynamic control during the initial N–C bond formation/cyclization reaction. The interaction between the oxygen atom of the sulfonyl group with the iron(III) chloride plays a key role in the final diastereoselectivity of the process. Finally, the utility of our *trans*-2,5-disubstituted azacycles synthesis is highlighted in an enantiodivergent approach towards the formal synthesis of both (+)- and (-)-pyrrolidine 197B alkaloids from *L*-glutamic acid. The extension of this methodology to the synthesis of 2,6-disubstituted piperidines is under development.

Experimental Section

General methods and computational details are given in the Supporting Information.

General procedure by the iron(III) chloride catalyzed Prins cyclization: To a solution of α-alkyl-*bis*-homoallyl tosylamine or α-alkyl-*bis*-homoallyl mesylamine (1.0 equiv) in anhydrous CH_2Cl_2 (0.1 M) at room temperature was added $FeCl_3$ in one portion. The reaction mixture was stirred at this temperature and monitored by TLC until complete formation of the corresponding heterocycle. The reaction was quenched by addition of water with stirring for 30 min, and the mixture extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulphate, filtered and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica gel column chromatography (*n*-hexane/EtOAc solvent systems).

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Keywords: intramolecular hydroamination • pyrrolidine • iron • proline • density functional calculations

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[21] Reaction time was set to 6h for 100 mol% of $FeCl_3$ whereas 15h were needed when 10 mol% of $FeCl_3$ was used.
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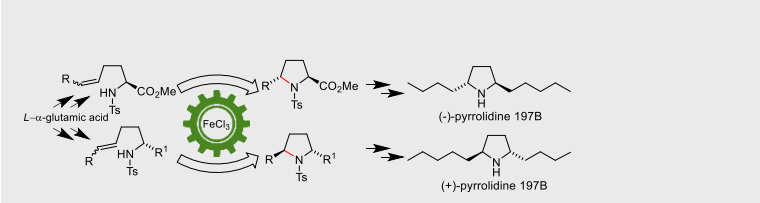

The green route to 5-membered ring azacycles: We have established an innovate method to obtain enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-proline derivatives. An enantiodivergent approach to the synthesis of both (+) and (-)-pyrrolidine 197B from *L*-glutamic acid is presented. Selectivity is explained by DFT.

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Enantiodivergent synthesis of (+)- and (-)-pyrrolidine 197B. Synthesis of *trans*-2,5-disubstituted pyrrolidines via Intramolecular hydroamination