ChemPubSoc Europe

DOI: 10.1002/chem.201602708

CHEMISTRY A European Journal Full Paper

Hydroamination

Enantiodivergent Synthesis of (+)- and (−)-Pyrrolidine 197B: Synthesis of *trans*-2,5-Disubstituted Pyrrolidines by 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 were synthesized by means of a 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 carried out to gain insight into the complete diastereoselectivity of the transformation.

Introduction

Five-membered azacycles are common structural units 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 proline residues or derivatives thereof, and drugs.[1–3]

Over the last decade, we have 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]

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, direct formation of these type of azacyles through an aza-Prins cyclization does not occur, which agrees with a disfavored 5-*endo*-trig cyclization according to Baldwin's rules (Scheme 2).[8, 9]

Therefore, the development of new methodologies allowing efficient and stereocontrolled access to these nitrogen heterocycles is a challenge for synthetic organic chemists. Among these methodologies, the intramolecular hydroamination reaction (IHR) has become nowadays one of the most powerful tools towards the synthesis of 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 hydroamination of alkenes is more difficult than that of alkynes because of the lower reactivity and electronic density of the C=C bond. Although enantioselective olefin hydroamination is 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

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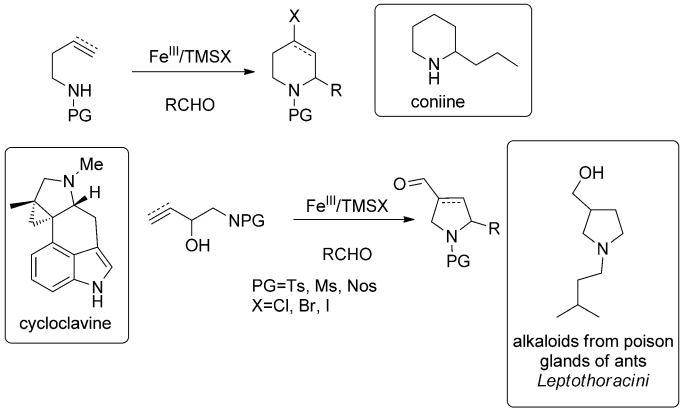
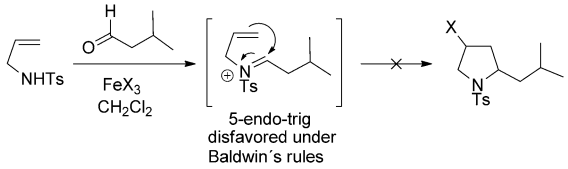
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201602708.



Scheme 1. Synthesis of five- and six membered azacycles, developed by us, and its application in natural product synthesis.



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

shortcoming by using a sustainable strategy that would combine an inexpensive and biorelevant metal with accessible and abundant enantiopure compounds, such as iron and amino acids, respectively.[12]

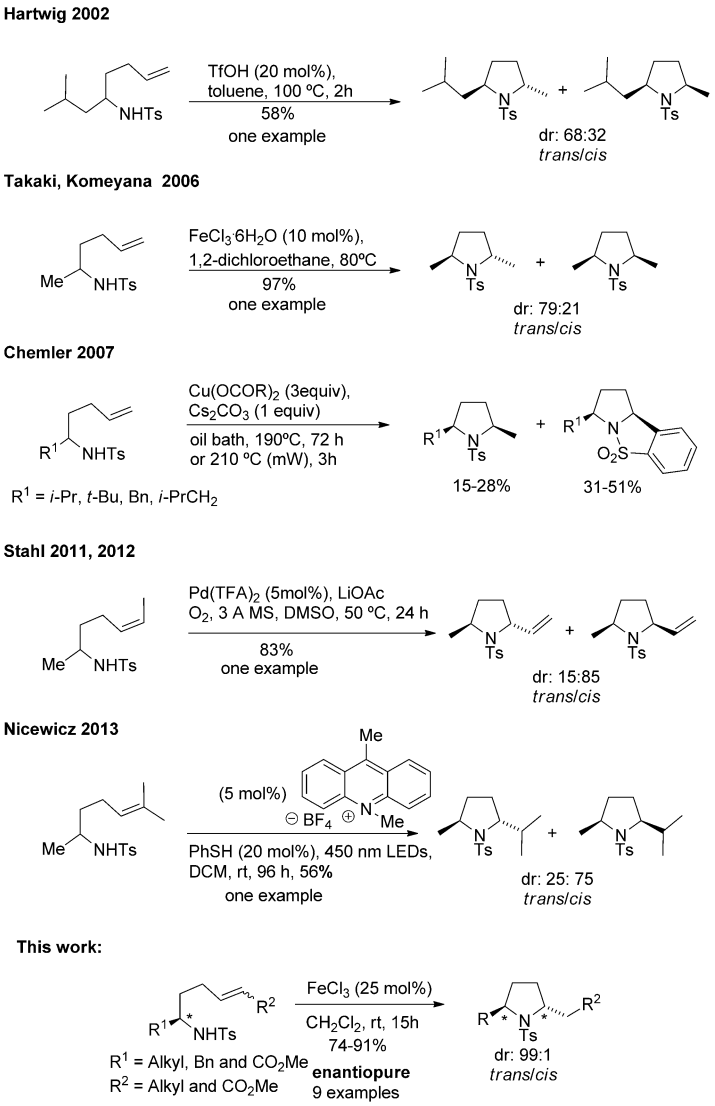
To the best of our knowledge, despite the enormous interest in iron catalysis and hydroamination reactions,[13] only a few examples of iron-catalyzed IHRs involving protected or unprotected amines and unactivated alkenes exist.[14] In these cases, the process involves primary aliphatic amines and leads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

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

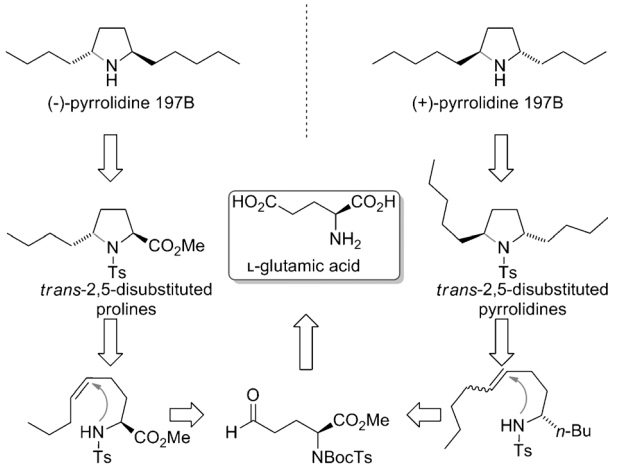
Results and Discussion

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

With the idea to find a fully diastereoselective synthesis of *trans*-2,5-disubstituted pyrrolidines as the basis 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 of initial reduction of the amino acid to the β-amino alcohol with $NaBH_4$ and iodine, followed by formation of the corresponding *N*-tosyl aziridines by sequential *O*-tosylation and intramolecular cyclization.[18a]

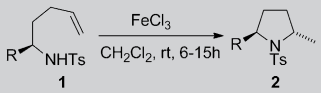


Scheme 3. Previous strategies and our work to access *trans*-2,5-disubstituted pyrrolidines.

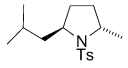
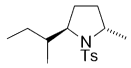
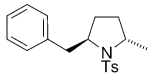


Scheme 4. Enantiodivergent strategy for the preparation of (+)- and (−)-pyrrolidine 197B.

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



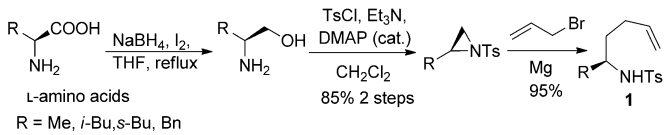
1 **2**

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

[a] Reaction conditions: **1** (1.0 mmol), $FeCl_3$, dry CH_2Cl_2 (0.1 M), RT, 6–15 h, open to air. Ts = *p*-toluenesulfonyl. [b] Yields of isolated products after purification by silica-gel column chromatography.

Finally, regioselective opening of the *N*-tosyl aziridine ring by treatment with allylmagnesium bromide afforded the *N*-tosyl bis-homoallyl amines **1** in very good yields (Scheme 5).

Thus, we began by treating (*S*)-*N*-(hex-5-en-2-yl)-tosylsulfonamide (**1**, R = Me) with an equimolecular amount of $FeCl_3$ (100 mol%) in dry dichloromethane at room temperature for



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

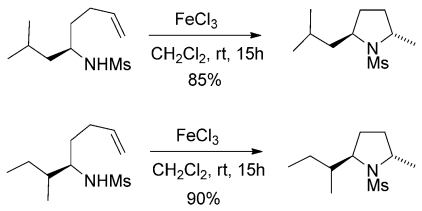
6 h. Under these reaction conditions, (2*S*, 5*S*)-2,5-dimethyl-1-tosylpyrrolidine (**2**) was isolated in quantitative yield (Table 1, entry 1). Cyclization of this α-methyl-substituted tosylaminopentene **1** therefore proceeded with excellent *trans* diastereoselectivity. Indeed, pyrrolidine **2** was isolated exclusively, and no traces of the corresponding *cis*-pyrrolidine isomer were detected in the crude reaction products.[20] The IHR also works well with different aliphatic α substituents and leads 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, also has no significant effect on the reaction yield (84%, Table 1, entry 4).[21] Decreasing the amount of $FeCl_3$ increased the reaction time but provoked only a slight decrease in the reaction yields, which was more evident when 10 mol% of $FeCl_3$ was used (see Table 1).[22] This IHR is thus a stereoselective cyclization reaction that exclusively affords the corresponding *trans*-pyrrolidine derivative regardless of the type of α substituents present in the initial sulfonylamino alkene and/or reaction conditions.

Theoretical calculations on iron(III)-catalyzed alkene IHR

Two different reaction mechanisms can be envisaged for this IHR: 1) a simple acid-catalyzed Markovnikov hydroamination through direct or indirect interaction with the alkene functionality[16a] and 2) direct participation of the transition metal moiety in the cyclization, which therefore controls the diastereoselectivity of the process. In our reactions, anhydrous $FeCl_3$ was used at room temperature, and formation of HCl was not expected. Furthermore, when the reactions were carried out in the presence of trimethylsilyl chloride (1 equiv), which 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 80 °C, which can produce Fe_2O_3 and HCl. In addition, HCl (30 mol%) and other catalysts, such as *p*-toluenesulfonic acid or/and phenylacetic acid, were also tested, with the 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 in accordance with the precedents highlighted in Scheme 3, the presence of the tosyl group is not translated into a fully diastereoselective process. Hartwig and Schlummer[16a] as well as Morimoto, Takaki, and Komeyama[14a] obtained low diastereoselectivity favoring the *trans*-pyrrolidines by using triflic acid and $FeCl_3 \cdot H_2O$, respectively, whereas Chemler, Stahl, and Nicewicz obtained the *cis*-pyrrolidines as major isomers using other catalysts based on copper, palladium, or an organic iminium salt.[16c,d]

In accordance with 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 of *p*-toluensulfonyl, Scheme 6). We synthesized the unsaturated *N*-mesyl analogues of **1** by the same synthetic sequence as described above (see



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

Scheme 5). The treatment of the isobutyl and *sec*-butyl bis-homoallyl mesylamines with $FeCl_3$ (1 equiv) led to the corresponding *trans* *N*-mesyl pyrrolidines in very good yields, that is, the volume of the substituent attached to the sulfonyl group has no direct influence on the diastereoselectivity of the IHR (Scheme 6).

The diastereoselectivity of the reaction was not affected by variation of the reaction temperature (refluxing or cooling), which only modifies the reaction time. Nevertheless, it seems that the tosyl or mesyl group is not a mere spectator in the process, as was confirmed by theoretical calculations. 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 (Figure 1).

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*** ($\Delta E^{\ddagger} = 14.5$ kcal mol^{-1}) in an endothermic reaction ($\Delta E_R = 12.4$ kcal mol^{-1}). The complete diastereoselectivity of the process arises under both kinetic and thermodynamic control, in view of the considerably higher activation energy ($\Delta E^{\ddagger} = 20.9$ kcal mol^{-1} via **TS1-*cis***) and endothermicity ($\Delta\Delta E_R = 5.1$ kcal mol^{-1}) associated with the formation of the alternative **INT1-*cis*** intermediate. 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 and thus facilitates 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 length 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 of 0.63 and 0.65 computed for the adjacent Fe–Cl bonds). 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** ($\Delta E_R = -2.2$ kcal mol^{-1}). The last step of the process involves protonolysis of the Fe–CH_2 bond in **INT2** promoted by HCl through the transition state **TS2** ($\Delta E^{\ddagger} = 11.8$ kcal mol^{-1}), a saddle point associated with Fe–C bond rupture/C–H bond formation). This transformation produces the $FeCl_3$-coordinated *trans*-pyrrolidine **INT3** in a highly exothermic reaction ($\Delta E_R = -41.7$ kcal mol^{-1}). 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 with the de-

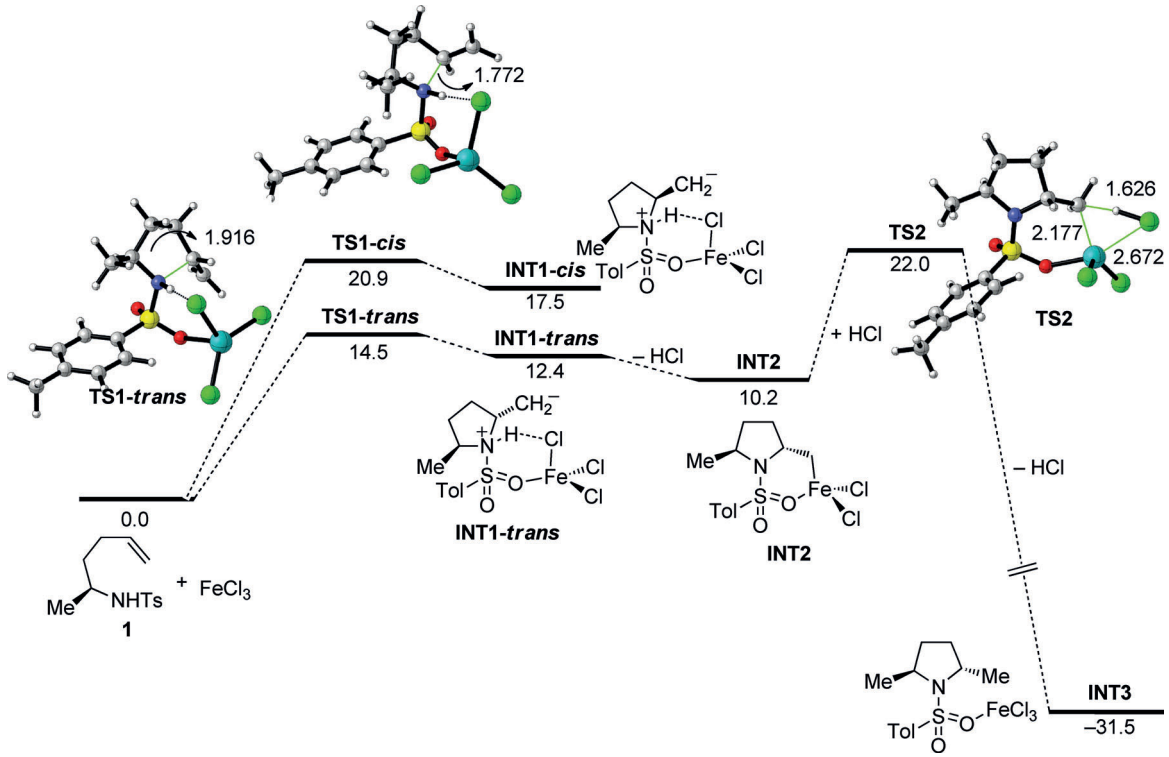
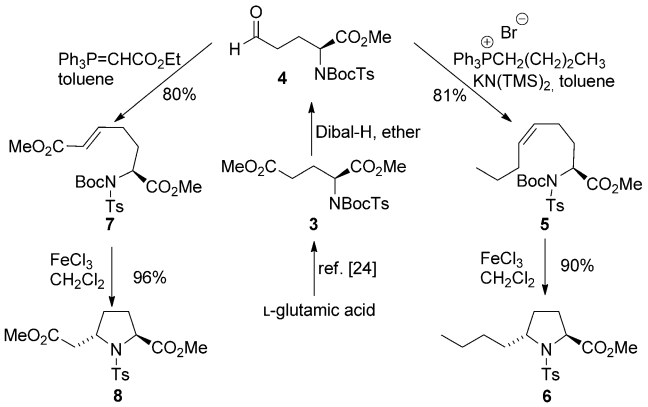


Figure 1. Computed reaction profiles for the reaction of tosylamino pentene **1** in the presence of $FeCl_3$. Relative electronic energies ΔE [kcal mol^{-1}], including zero-point vibrational energy, and bond lengths [Å] are given. All data were computed at the PCM(CH_2Cl_2)–M06/def2-TZVP//M06/def2-SVP level of theory.

coordination of $FeCl_3$ in **INT3**, which would enter in a new catalytic cycle and release 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).

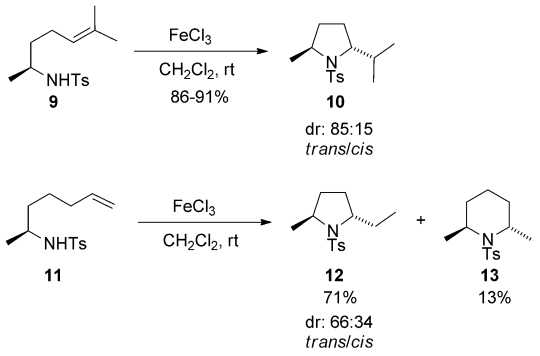


Scheme 7. Diastereoselective intramolecular hydroamination. Synthesis of *trans*-5-substituted proline derivatives. Boc = *tert*-butoxycarbonyl.

The Wittig olefination of aldehyde **4** with 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 by means of 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 complements the known syntheses of 5-substituted prolines based, among others, on Strecker-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 skeletons,[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). Under optimized conditions (Table 1), we treated

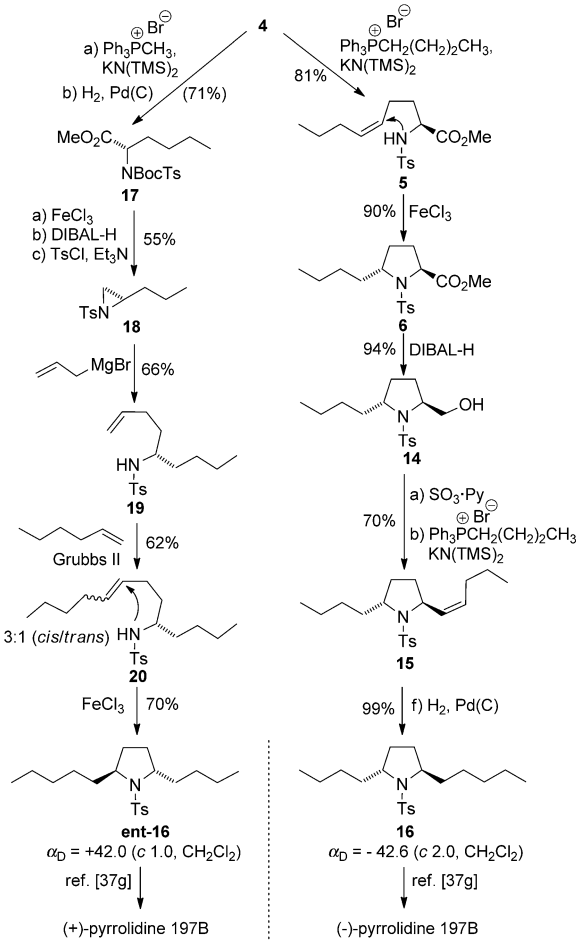


Scheme 8. IHR of tosylamino alkenes with trisubstituted double bond and and a longer aliphatic chain.

both compounds with 25 and 100 mol% $FeCl_3$. As shown in Scheme 8, 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 well under catalytic or stoichiometric conditions (86% for 25 mol% and 91% for 100 mol% $FeCl_3$). 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 rings, whereby the 2,5-*trans* pyrrolidine is the preferred reaction product. This behavior is similar to that observed by Takaki, Komeyana, and Morimoto and might be caused by 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 for the synthesis of enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-substituted proline derivatives in hand, we decided to synthesize the alkaloids (+)- and (−)-pyrrolidine 197B by 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 via the *trans*-5-substituted proline pathway, in which the α-substituent ester group was modified after the intramolecular hydroamination/cyclization reaction. Homologation of aldehyde **4** through Wittig olefination and *N*-Boc deprotection/IHR promoted by iron(III) chloride 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**, in which the aliphatic chain was then installed (Scheme 9). This linear aliphatic chain was generated in a three-step reaction sequence involving Parikh–Doering oxidation, Wittig reaction with unstabilized ylide, and final hydrogenation of *cis*-olefin **15**. The resulting (2*R*, 5*R*)-2-butyl-5-pentyl-1-tosylpyrrolidine (**16**) constitutes the Davis intermediate to one step away from the (−)-pyrrolidine 197B synthesis.[37g]

For synthesis of the (+)-enantiomer, the ester at the α position was modified before IHR in the *trans*-2,5 pyrrolidine pathway. Again, we started with a Wittig reaction of aldehyde **4**



Scheme 9. Formal synthesis of (+)- and (−)-pyrrolidine 197B. DIBAL-H = diisobutylaluminum hydride

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 to the final IHR, the second aliphatic side chain was installed by an alkene-metathesis reaction. Finally, the *trans*-*N*-tosyl pyrrolidine **ent-16** was obtained by the iron(III) chloride-promoted IHR in excellent yield. This again confirmed that the final stereochemistry of **ent-16** does not depend on the stereochemistry of the double bond in **20**. Compared to previous syntheses, our enantiodivergent approach to (+)- and (−)-pyrrolidine 197B is much shorter than the only other enantiodivergent approach, reported by Machinaga and Kibayashi. Our syntheses required nine and seven steps, respectively. In contrast, their syntheses required 16 steps starting from C_2-symmetric diepoxides derived from D-mannitol.[37a,b] Concerning the synthesis of (+)-pyrrolidine 197B, to the best of our knowledge, our approach with nine steps is at the same level as the best published syntheses, by Takahata, Ohkubo, and Momose (ten steps),[37c] Mandille et al. (eight steps),[37d] and Marks et al. (ten steps).[37e] With respect to the preparation of (−)-pyrrolidine 197B, our approach is the shortest synthesis reported to date, besides those of Lhommet et al. (eight steps) and Davis et al. (seven steps).[37f,g]

Conclusion

We have established a new method to obtain enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-substituted proline derivatives by means of a combination of an iron(III) salt, as a sustainable metal catalyst, and enantiopure α-amino acids. A completely diastereoselective iron-catalyzed intramolecular hydroamination/cyclization reaction involving α-substituted amino alkenes in an enantiomeric context was thus described. According to DFT calculations, the complete diastereoselectivity of the process arises 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 and iron(III) chloride plays a key role in the final diastereoselectivity of the process. Finally, the utility of our synthesis of *trans*-2,5-disubstituted azacycles was highlighted by 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 for $FeCl_3$-catalyzed Prins cyclization

$FeCl_3$ was added in one portion 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. 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 and stirring for 30 min, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried with magnesium sulfate, filtered, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash silica-gel column chromatography (*n*-hexane/EtOAc).

Acknowledgements

This research was supported by the Spanish MINECO, co-financed by the European Regional Development Fund (ERDF) (CTQ2014-56362-C2-1-P, CTQ2013-44303-P). S.J.P. and D.A.C thanks the Spanish MINECO for an F.P.U and an F.P.I fellowship, respectively. J.M.L.-S. thanks the Fundación CajaCanarias-Obra

Social La Caixa for a fellowship. The ORFEO-CINQA network is also acknowledged.

Keywords: alkaloids · cyclization · hydroamination · iron · nitrogen heterocycles

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

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Received: June 7, 2016
Published online on ■■ ■■, 0000

FULL PAPER

Hydroamination

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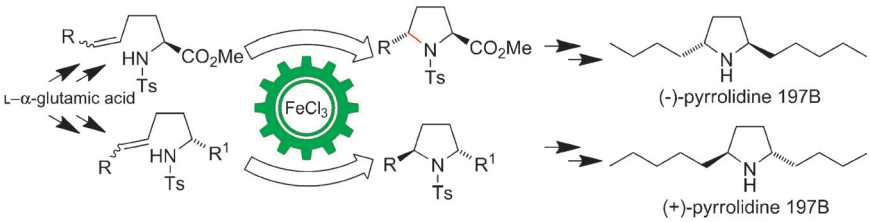
Enantiodivergent Synthesis of (+)- and (−)-Pyrrolidine 197B: Synthesis of *trans*-2,5-Disubstituted Pyrrolidines by Intramolecular Hydroamination



Green route to 5-membered azacycles: An innovative method to obtain enantiopure *trans*-2,5-disubstituted pyrrolidines and *trans*-5-proline derivatives was established. An enantiodivergent approach to the synthesis of both (+)- and (−)-pyrrolidine 197B from L-glutamic acid is presented (see scheme). The selectivity was explained by DFT calculations.