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$FeCl_3$-Catalyzed Highly Diastereoselective Synthesis of Substituted Piperidines and Tetrahydropyrans

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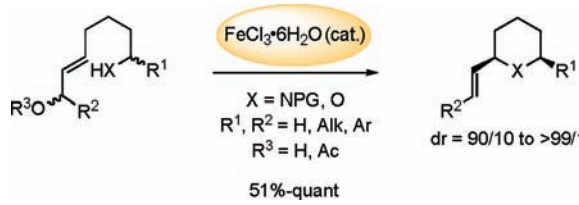
ABSTRACT



The eco-friendly and highly diastereoselective synthesis of substituted *cis*-2,6-piperidines and *cis*-2,6-tetrahydropyrans is described. The key step of this method is the iron-catalyzed thermodynamic equilibration of 2-alkenyl 6-substituted piperidines and 2-alkenyl 6-substituted tetrahydropyrans allowing the isolation of enriched mixtures of the most stable *cis*-isomers.

Nitrogen- and oxygen-containing heterocyclic frameworks are ubiquitous subunits in biologically active products.[1−3] Although convenient methods for the construction of substituted piperidines[2] and tetrahydropyrans[2b,3] exist, the development of highly stereoselective and eco-friendly reactions to access these heterocycles remains a great challenge.

The metal-catalyzed activation of allylic, propargylic, or benzylic alcohols is of outstanding importance in organic synthesis.[4−6] Indeed, this process is particularly interesting from both an atom-economy and eco-friendly point of view as water is the only byproduct formed when a reaction is performed in the presence of a nucleophile such as NuH. Among the different metal salt catalysts used, the low-toxic and inexpensive $FeCl_3$ is known to activate allylic, propargylic, and benzylic alcohols or acetate derivatives toward the addition of various nucleophiles such as arenes,[7] indoles,[8] or active methylene compounds.[9] It is worth mentioning that only a few examples involving nitrogen[7b,10] and oxygen[5q,7b,11] nucleophiles have been reported.[12]

Among the existing methods to form piperidines and tetrahydropyrans **B**, the metal-catalyzed cyclization of ζ-amino and ζ-hydroxy allylic alcohol derivatives **A** using mercury,[13] palladium,[14] iridium,[15] or gold complexes[16] is an attractive strategy. Herein, we report that $FeCl_3$ is able to catalyze the cyclization of allylic substrate **A** to produce substituted piperidines (X = NPG) and tetrahydropyrans (X = O) **B** with high diastereoselectivities (Scheme 1).

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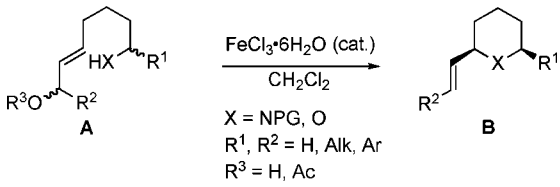
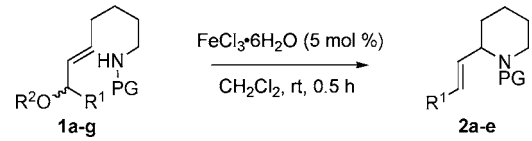
Scheme 1. $FeCl_3$-Catalyzed Cyclization of ζ-Amino and ζ-Hydroxy Allylic Alcohol Derivatives (PG = Protective Group)



The reactivity of *N*-protected ζ-amino allylic alcohol derivatives **1a**−**g** (R^2 = H) was examined first (Table 1). When the *N*-protected ζ-amino allylic acetates **1a**−**c** were treated with $FeCl_3$•$6H_2O$ (5 mol %) in CH_2Cl_2 at rt, a smooth and fast reaction took place and the corresponding mono-substituted piperidines **2a**−**c** were isolated in good to excellent yields (65−99%).[17] The best result was obtained when the *N*-tosyl protecting group was used (99% yield) (Table 1, entry 3).[18] The influence of the allylic substituent R^1 on the outcome of the cyclization was then investigated. Replacing the phenyl substituent with a methyl group such as in **1d** virtually did not affect the reactivity of the substrate as piperidine **2d** was obtained in 96% yield (Table 1, entry 4). The strong activating influence of the allylic substituent became obvious when the latter was completely removed. Indeed, the yield in piperidine **2e** obtained from the cylization of primary allylic acetate **1e** dropped to 61% (Table 1, entry 5). The reactivity of ζ-amino allylic alcohols and acetates was found to be similar; when **1f** (R^1 = Ph) was treated with 5 mol % of $FeCl_3$•$6H_2O$, **2c** was isolated in good yield (95%) (Table 1, entry 6), whereas under the same conditions, **1g** was poorly reactive even with 40 mol % of $FeCl_3$•$6H_2O$ (16% yield) (Table 1, entry 7).

Table 1. $FeCl_3$-Catalyzed Synthesis of 2-Alkenylpiperidines



entry	PG	R^1	R^2	**1**	**2**	yield[a] (%)
1	Boc	Ph	Ac	**1a**	**2a**	72
2	CBz	Ph	Ac	**1b**	**2b**	65
3	Ts	Ph	Ac	**1c**	**2c**	99
4	Ts	Me	Ac	**1d**	**2d**	96
5	Ts	H	Ac	**1e**	**2e**	61
6	Ts	Ph	H	**1f**	**2c**	95
7	Ts	H	H	**1g**	**2e**	16[b]

[a] Isolated yields. [b] $FeCl_3$•$6H_2O$ (40 mol %), CH_2Cl_2, rt, 18 h.

The reaction was generalized concerning *N*-protected ζ-amino allylic acetates **3a**−**g** in order to access

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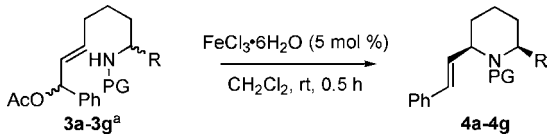
(17) In the case of compound **1c**, anhydrous $FeCl_3$ was also evaluated in order to catalyze the cyclization and lead to the same result as observed with the more easy-to-handle hexahydrate.

2,6-disubstituted piperidines (X = NPG, $R^2 \neq H$)[19] (Scheme 1), and the results are summarized in Table 2.

Table 2. $FeCl_3$-Catalyzed Synthesis of *cis*-2,6-Piperidines

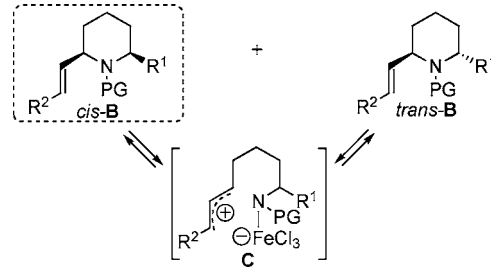


entry	PG	R	3	4	yield[b] (%)	dr[c]
1	Ts	*i*-Pr	**3a**	**4a**	99	>99/1
2	Ts	*n*-C_5H_{13}	**3b**	**4b**	70	97/3
3	Ts	Me	**3c**	**4c**	80	92/8
4	Ts	Ph	**3d**	**4d**	80	90/10
5	Boc	*i*-Pr	**3e**	**4e**	66[d]	>99/1
6	CBz	*i*-Pr	**3f**	**4f**	66	>99/1
7	Ns	*i*-Pr	**3g**	**4g**	90[e]	>99/1[e]
8	Ns	*i*-Pr	**3g**	**4g**	90[f]	50/50[f]

[a] Mixture of diastereoisomers. [b] Isolated yields. [c] Determined by ^1H NMR. [d] rt, 6 h. [e] $FeCl_3$•$6H_2O$ (10 mol %), rt, 10 h. [f] rt, 2 h. Ns = *o*-nitrobenzenesulfonyl.

As *N*-tosyl derivatives previously exhibited the best reactivity, they were first examined (Table 2, entries 1−4). The R substituent has a low influence on the cyclization process as compounds **3a**−**d** were transformed to the corresponding *cis*-2,6-piperidines **4a**−**d** in good yields (up to 80%) and high diastereoselectivities in favor of the *cis*-diastereoisomers (*cis*/*trans* from 90/10 to 99/1).[20] In order to investigate the influence of the *N*-protecting group (PG = Boc, Cbz, Ns) on the diastereoselectivity of the cyclization, various substrates bearing an isopropyl substituent (R = *i*-Pr) were treated with $FeCl_3$•$6H_2O$ (Table 2, entries 5−7). In all cases, the diastereoselectivity was excellent as the *N*-protected *cis*-2,6-disubstituted piperidines **4e**−**g** were isolated as a single diastereoisomer (Table 2, entries 5−7).[20] However, in the presence of a nosyl group (**3g**), longer reaction times and higher catalyst loadings (10 mol %) were required to reach high diastereoselectivity (dr >99/1) (Table 2, entry 7). Indeed, when **3g** was treated with 5 mol % of $FeCl_3$•$6H_2O$, after 2 h at rt, piperidine **4g** was isolated as a 1/1 diastereomeric mixture (Table 2, entry 8). Intrigued by this last result, a 1/1 mixture of *cis*-**4g** and *trans*-**4g** was treated with $FeCl_3$•$6H_2O$ (10 mol %), and interestingly, piperidine *cis*-**4g** was isolated as the sole diastereoisomer after 10 h at rt (dr >99/1). This observation indicates that epimerization of the piperidine occurs in the presence of $FeCl_3$•$6H_2O$, leading to the thermodynamically most stable *cis*-isomer. This epimerization can be explained by the formation of a zwitterion intermediate **C** (Scheme 2). In addition, when the optically active acetate (*R*)-**1c** was treated with $FeCl_3$•$6H_2O$, the corresponding piperidine **2c** was obtained as a racemate, thus supporting the hypothesis of a carbocation intermediate.

Scheme 2. $FeCl_3$-Mediated Epimerization of *N*-Protected 2-Alkenylpiperidines



In order to demonstrate the broad scope of this reaction, the $FeCl_3$-catalyzed heterocyclization process was applied to ζ-hydroxy allylic alcohols and acetates **A** (X = O) (Scheme 1) to form 2,6-disubstituted tetrahydropyrans of type **B**.[21] Treatment of **5a** with $FeCl_3$•$6H_2O$ produced the expected tetrahydropyran **6a** in good yield (Table 3, entry 1). In order to study the diastereoselectivty of the reaction, various derivatives **5b**−**h** were screened. When substrate **5b** bearing a phenyl group at the allylic position was treated with $FeCl_3$•$6H_2O$, the corresponding tetrahydropyran **6b** was isolated with an excellent diastereomeric ratio of 97/3 in favor of the *cis*-isomer (Table 3, entry 2).[22] The reaction is general as different aryl groups such as phenyl and mesityl (Mes) can be present at the allylic position, and various alkyl groups (*n*-C_5H_{11}, *i*-Pr, Me) or an electron-withdrawing group (CO_2Me) are tolerated as R^1 substituent (Table 3, entries 2−6). In all cases, *cis*-2,6-tetrahydropyrans were obtained in good yields (up to 82%) and with excellent diastereoselectivities (90/10 to 98/2). The change from a phenyl group to a mesityl group at the allylic position shortened the reaction time, while similar yields and diastereoselectivities were obtained (Table 3, entries 3 and 4). Furthermore, the chiral alcohol (1*RS*,7*R*)-**5e** furnished the optically active tetrahydropyran (*R*,*R*)-**6e** with excellent diastereoselectivity and enantiomeric excess (ee >98%, Table 3, entry 5).[23] Nonbenzylic secondary and tertiary allylic alcohols such as **5g** and **5h** are also excellent substrates for synthesizing *cis*-2,6-tetrahydropyrans as **6g** and **6h** were isolated in good yields and with diastereoselectivities up to 97/3 (Table 3, entries 7 and 8). It is worth mentioning that the formation of tetrahydropyran **6h** required an additional 5 mol % of catalyst and 24 h of reaction; after 5.5 h, a poor 52/48 dr

(18) When the *N*-benzyl-protected substrate **1** (R1 = Ph, R2 = Ac) was treated with 25 mol % of $FeCl_3$•$6H_2O$ at rt in CH_2Cl_2, no conversion was observed.

(19) Due to synthetic purposes, *N*-protected ζ-amino allylic acetates were used in this study rather than the corresponding *N*-protected ζ-amino allylic alcohols. See the Supporting Information for details.

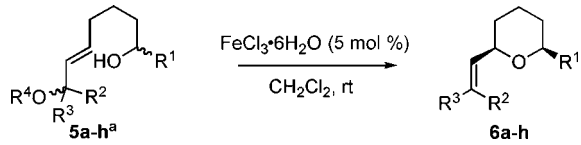
(20) The *cis*-relationship for piperidine **4a** was unambiguously established by X-ray structure analysis. See the Supporting Information for details. The *cis*-relationship for piperidines **4b**−**g** was assigned by comparison with piperidine **4a**.

(21) Similar allylic substrates have been previously used for related cyclizations using Pd, Ir, or Au catalysts; see refs 3c, 15b, and 16.

(22) The *cis*-relationship was confirmed by NOE experiments for tetrahydropyrans **6b**, **6d**, **6g**, and **6i**.

(23) (1*RS*,7*R*)-**5e** was prepared from the commercially available (*R*)-propylene oxide (ee >98%).

Table 3. $FeCl_3$-Catalyzed Synthesis of *cis*-2,6-Tetrahydropyrans



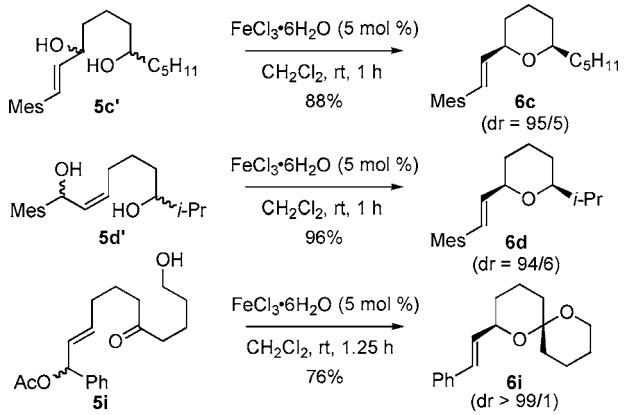
entry	R^1	R^2, R^3, R^4	**5**	**6**	yield[b] (%) (time, h)	dr[c]
1	H	Ph, H, H	**5a**	**6a**	81 (0.5)	
2	n-C_5H_{13}	Ph, H, H	**5b**	**6b**[d]	83 (2)	97/3
3	n-C_5H_{13}	Mes, H, H	**5c**	**6c**	89 (1)	95/5
4	i-Pr	Mes, H, H	**5d**	**6d**[d]	82 (1)	95/5
5	Me	Mes, H, H	(1*RS*,7*R*)-**5e**	(*R*,*R*)-**6e**	51 (1)	98/2
6	CO_2Et	Ph, H, Ac	**5f**	**6f**	quant (48)[e]	90/10[e]
7	n-C_5H_{13}	Me, Me, H	**5g**	**6g**[d]	87 (0.25)	91/9
8	n-C_5H_{13}	Me, H, H	**5h**	**6h**	82 (24)[f]	97/3[f]

[a] Mixture of diastereoisomers. [b] Isolated yields. [c] Determined by ^1H NMR or by GC/MS analysis. [d] 2,6-*Cis*-relationship confirmed by NOE studies. [e] $FeCl_3$•$6H_2O$ (15 mol %), rt. [f] An additional 5 mol % of $FeCl_3$•$6H_2O$ was added after 5.5 h when the dr was 52/48.

was observed. The latter result serves to illustrate the remarkable capacity of $FeCl_3$ to equilibrate 2-alkenyl-6-alkyltetrahydropyrans.

In contrast to the Au-catalyzed formation of 2,6-tetrahydropyrans which proceeds through an S_N2' pathway,[16a] $FeCl_3$•$6H_2O$ is able to catalyze the cyclization of 1,5-monoallylic diols. Indeed, when **5c′** was treated with $FeCl_3$•$6H_2O$, tetrahydropyran **6c** was obtained with the same diastereoselectivity as the one obtained from **5c** (Scheme 3 and Table 3, entry 3). Additionally, the (*E*)-configuration of the double bond of the allylic alcohol in **5d** or the (*Z*)-configuration in **5d′** has no influence on the *cis*/*trans* ratio of the obtained tetrahydropyran, probably due to the formation of a carbocation intermediate (Scheme 3).[12d,e] Interestingly, spiroketal **6i** was formed from the corresponding hydroxyketone **5i** in good yield and with excellent diastereoselectivity (Scheme 3).[24,22]

Scheme 3



In summary, we have developed an eco-friendly and highly diastereoselective synthesis of *cis*-2,6-disubstituted piperidines and *cis*-2,6-disubstituted tetrahydropyrans, which are valuable building blocks for the synthesis of biologically active targets. The mild catalytic conditions developed allowed the use of substrates bearing alkyl or ester groups. The thermodynamic epimerization of the produced 2-alkenyl 6-substituted piperidines and 2-alkenyl 6-substituted tetrahydropyrans induced by $FeCl_3$ is the key to account for the high diastereoselectivities observed in favor of the most stable *cis*-isomers.

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Supporting Information Available: General procedure for the heterocyclization reactions, substrate preparation, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) In this case, the equilibration conditions led to the formation of the most stable spiroketal resulting from double anomeric stabilization.