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Iron Catalysis

Iron-Catalyzed Synthesis of α-Dienyl Five- and Six-Membered N-Heterocycles

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Abstract: The iron-catalyzed synthesis of α-dienyl N-heterocycles is reported. The method is cost-effective, atom-economic, and led to a range of substituted α-dienyl heterocycles in moderate to good yields and diastereoselectivities. The α-dienyl piperidines are key synthetic intermediates as demonstrated by the preparation of a panel of α-polyenyl N-heterocycles.

Introduction

Five- and six-membered ring N-heterocycles are present in a myriad of bioactive natural products[1] and among them, α-polyenyl-substituted piperidines constitute an important class of alkaloids. For example, corydendramine A and B,[2] microgrewiapine A,[3] and microcosamine A and B[4] are trisubstituted piperidines that only differ by the nature of the *N*- and polyenyl substituents. Microgrewiapine A is an antagonist of some nicotinic receptors, whereas microcosamine A and B display insecticidal activity. Alkaloid (–)-SS20846A is another example of bioactive α-dienyl piperidine that possesses antibacterial and anticonvulsant properties.[5] (+)-Dienomycin C is a α-dienyl trisubstituted piperidine that exhibits a moderate antibiotic activity against *Mycobacteria* (Figure 1).[6]

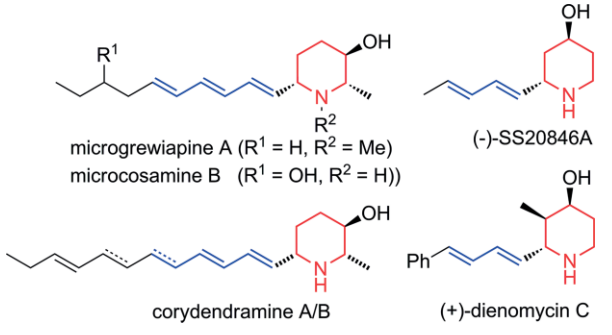
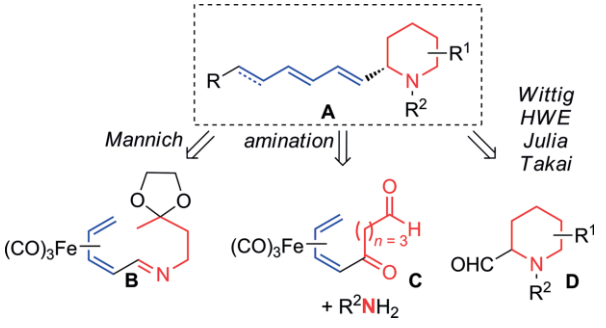


Figure 1. Bioactive α-polyenyl piperidines.

As a result of their biological and pharmacological properties, these α-polyenyl-substituted piperidines have attracted organic chemists and numerous syntheses of these compounds have been described over the last decades. However, examination of the literature does not bring out a general method for the construction of α-polyenyl-substituted piperidines. Intramolecular Mannich reaction of iminoacetals that already incorporate a protected diene has been used to access α-dienyl piperidines.[7] These cyclization reactions generally required relatively harsh acidic conditions and high temperatures. One example of double amination between a keto-aldehyde with the coordinated diene motif and a primary amine were also reported to synthesize the substituted N-heterocycles.[8,9] In most syntheses, the polyenic fragment is introduced at a late stage generally from piperidino-aldehydes **D**. Wittig, Horner–Wadsworth–Emmons (HWE), and Julia olefination reactions are commonly employed but mixtures of (*E*,*E*)- and (*E*,*Z*)-dienes are often observed.[10,11] This lack of stereocontrol associated with the formation of stoichiometric amounts of by-products generally result in moderate yields and troublesome purifications (Scheme 1).



Scheme 1. Access to α-polyenyl piperidines.

Consequently, the development of synthetic methods to access α-polyenyl-substituted N-heterocycles is still desirable. In the field of N-heterocycle synthesis by construction of the C–N bond, metal-catalyzed cyclization of amino allylic alcohol derivatives of type **E** is particularly attractive in terms of atom-economy and eco-compatibility. Thus, Pd^0-,[12] Pd^{II}-,[13] Ir-[14] and Au-[15]catalyzed cyclization reactions have been used as key steps in the synthesis of several N-heterocyclic alkaloids.[16] In 2010, our group reported the $FeCl_3$-catalyzed synthesis of piperidines from intermediates **E** (Scheme 2).[17a] The reaction generally proceeds smoothly with good diastereocontrol and was

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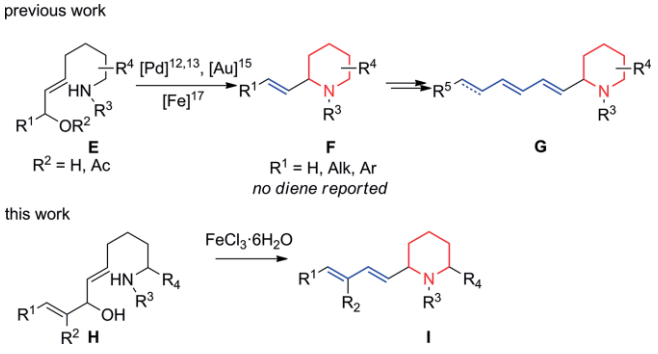
then extended to the formation of various heterocycles.[17b] The presence of the pendant double bond on cyclized products **F** offers functionalization opportunities. Notably, some α-polyenyl piperidines were prepared from this intermediate after ozonolysis or oxidative cleavage of the alkene followed by olefination.[18] In contrast, to our knowledge, no direct metal-catalyzed formation of α-dienyl-substituted N-heterocycles from amino dienes **H** has been reported so far. Herein, we report a $FeCl_3$-catalyzed synthesis of α-dienyl-substituted N-heterocycles (Scheme 2). The synthetic utility of the method is highlighted by the subsequent formation of various α-polyenyl N-heterocycles.

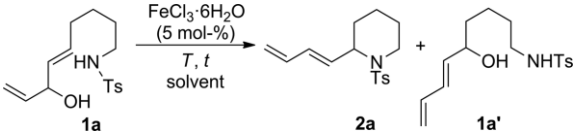


Scheme 2. Metal-catalyzed cyclization of amino allylic alcohol derivatives **E** and **H**.

Results and Discussion

The formation of α-dienyl monosubstituted piperidines from diene **1a** was first investigated to establish the optimized conditions. Based on our previous work, the reaction was carried out with a catalytic amount of $FeCl_3$·$6H_2O$ (5 mol-%) in CH_2Cl_2.[19] After 17 h at room temp., the cyclized product was isolated in a moderate yield of 61 % and only the (*E*)-isomer was observed (Table 1, Entry 1). Monitoring the reaction by GC/MS revealed that complete conversion of **1a** could be obtained after just 10 min (Table 1, Entry 2). The desired product was formed in a similar yield to the one obtained after 17 h at room temp. (62 %). Interestingly, diene **1a′** that resulted from an isomerization of the starting material was also isolated (20 %). When **1a′** was treated with $FeCl_3$·$6H_2O$ at room temp., the cyclization reaction was sluggish and produced substituted piperidine **2a** in 46 % yield after 2 h (data not shown). Even if **1a′** can led to piperidine **2a**, its formation appears detrimental to the cyclization process, hypothetically upon coordination of the amino-alcohol moiety to the iron center and subsequent poisoning of the catalyst. Because the formation of diene **1a′** from **1a** could result from the presence of water in the reaction medium, the cyclization was performed with anhydrous $FeCl_3$ (Table 1, Entry 2). Pleasingly, α-dienyl piperidine **2a** was obtained in a good yield of 73 %. Interestingly, the same yield of 73 % could be reached in the presence of easy-to-handle $FeCl_3$·$6H_2O$ by increasing the temperature to 50 °C (Table 1, Entry 3). Under these conditions, no conjugated diene **1a′** was detected after 10 min. We hypothesized that heat may either accelerate the cyclization of **1a**, which would avoid its isomerization to **1a′**, or facilitate the cyclization of conjugated diene **1a′** to **2a**. Work realized at higher temperatures (75 and 100 °C) in 1,2-dichloroethane did not improve the yield of **2a** (Table 1, Entries 4 and 5).[20] The influence of the solvent was then examined and, to our delight, the reaction carried out at room temp. in CH_3CN gave an excellent yield of 93 % of **2a** (Table 1, Entry 6).[21] From all these results, CH_2Cl_2 and CH_3CN were selected and the scope of the iron-catalyzed cyclization was examined.

Table 1. Optimization studies for the cyclization of **1a**.

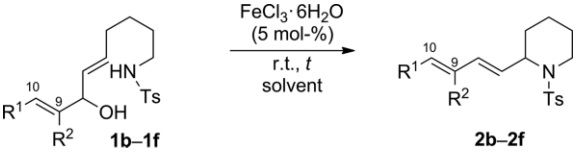


Entry	*t*	*T* [°C]	Solvent	**2a** (yield)	**1a′** (yield)
1	17 h	r.t.	CH_2Cl_2	61 %	0 %
2	10 min	r.t.	CH_2Cl_2	62 %, 73 %[a]	20 %, 0 %
3	10 min	50	CH_2Cl_2	73 %	0 %
4	10 min	75	$(CH_2)_2Cl_2$	57 %	0 %
5	10 min	100	$(CH_2)_2Cl_2$	69 %	0 %
6	17 h	r.t.	CH_3CN	93 %	0 %

[a] Anhydrous $FeCl_3$ was used.

Various dienes differing by their substitution pattern on the C9–C10 double bond were subjected to the cyclization conditions that have been tuned previously. The cyclization was not restricted to terminal diene as a methyl substituent (R^1 = Me, R^2 = H) was well tolerated (Table 2, Entry 1). The corresponding piperidine was isolated in good to excellent yield depending on the solvent with an unchanged (*E*)/(*Z*) ratio for the C9–C10 double bond. When the methyl was replaced by a phenyl group, the yield remained satisfying in CH_2Cl_2 (73 %) but dropped in CH_3CN (58 %; Table 2, Entry 2).[22] Pleasingly, functionalized α-dienyl piperidines that possess either an alkenyl iodide or an alkenyl tributylstannane could be accessed upon cyclization of the corresponding dienes (Table 2, Entries 3 and

Table 2. Synthesis of α-dienyl monosubstituted piperidines.

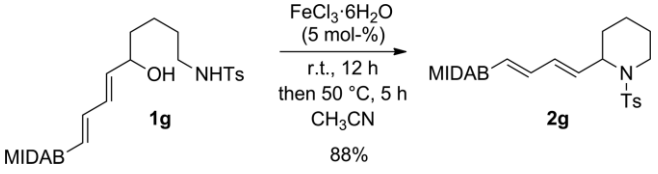


Entry	**1**	R^1	R^2	*t*	Solvent	**2** (yield)
1	**1b**[a]	Me	H	17 h	CH_2Cl_2	**2b** (74 %)[b]
				17 h	CH_3CN	**2b** (95 %)[b]
2	**1c**	Ph	H	17 h	CH_2Cl_2	**2c** (73 %)
				17 h	CH_3CN	**2c** (58 %)
3	**1d**	I	H	1 h	CH_2Cl_2	**2d** (78 %)
				18 h	CH_3CN	**2d** (59 %)
4	**1e**	$SnBu_3$	H	2 h	CH_2Cl_2	**2e** (56 %)
				2 h	CH_3CN	**2e** (66 %)
5	**1f**	H	Me	17 h	CH_2Cl_2	**2f** (70 %)
				17 h	CH_3CN	**2f** (88 %)

[a] Prepared as a 1:1 (*E*)/(*Z*) mixture for the C9–C10 double bond. [b] Obtained as a 1:1 (*E*)/(*Z*) mixture for the C9–C10 double bond.

4). These products could be considered as key intermediates toward the formation of α-polyenyl piperidines (vide infra). Interestingly, in all cases (Table 2, Entries 2–4), the reaction was selective toward the formation of the (*E*,*E*)-isomer. In the presence of a C9 substituent (R^2 = Me), the cyclization proceeded smoothly to deliver the corresponding piperidine in 88 % yield in CH_3CN (Table 2, Entry 5).

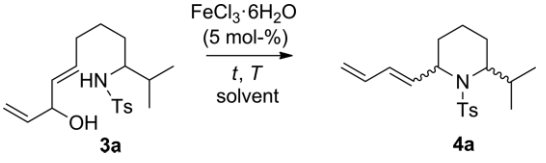
With the objective of accessing valuable synthons that could be transformed into α-polyenyl piperidines, diene **1g**, which features an *N*-methyliminoacetic acid (MIDA) boronate, was prepared. As a result of synthetic concerns the conjugated diene was prepared.[23] When **1g** was treated with $FeCl_3·6H_2O$ in CH_3CN at room temp., the reaction was slow and did not go to completion after 12 h.[24] However, by heating the reaction at 50 °C for an additional 5 h, total consumption of the starting diene occurred and the desired piperidine was isolated in a good yield of 88 % (Scheme 3).



Scheme 3. Access to a BMIDA-containing α-dienyl piperidine.

Encouraged by these positive results, we then turned our attention toward the synthesis of 2,6-disubstituted piperidines. The reactivity of amino-dienol **3a** was examined and, as the diastereoselectivity of the cyclization came into play, optimization of the conditions proved to be necessary. The previous study on the formation of monosubstituted α-dienyl piperidines showed that the solvent has an important influence on the outcome of the reaction and, consequently, a range of solvents was evaluated. In CH_2Cl_2, after 17 h at room temp., the expected piperidine was obtained in an excellent diastereomeric ratio of 96:4 in favor of the *cis* product albeit in a moderate yield of 63 % (Table 3, Entry 1).[25] The use of CH_3CN instead of CH_2Cl_2 completely modified the diastereoselectivity of the cyclization. After 17 h at room temp., an equimolar ratio of *cis*- and *trans*-piperidine **4a** was observed. Interestingly, by heating the reaction mixture, the diastereomeric ratio improved and after additional 52 h at 50 °C, *cis*-**4a** was formed as the major product (*dr* = 83:17) in a good yield of 84 % (Table 3, Entries 2 and 3). To account for this observation, we hypothesized that the increased temperature may facilitate an iron-induced equilibration process between the *cis*- and *trans*-piperidine, which might be inhibited at room temp. in CH_3CN. The equilibrium favors the formation of the most stable *cis*-diastereomer (vide supra). Worthy of note, when the mixture of *cis*-**4a** and *trans*-**4a** (*cis*/*trans* = 83:17) previously obtained in CH_3CN was treated again with $FeCl_3·6H_2O$ in CH_2Cl_2, a significant increase of the diastereomeric ratio was observed (*dr* > 97:3 after 12 h at room temp.). Unfortunately, this improved diastereoselectivity went along with a drop in isolated yield (51 %, see Supporting Information for details). As the formation of cationic intermediates was hypothesized (vide infra), the reaction was tested in highly ionizing 2,2,2-trifluoroethanol (TFE). Under these conditions, the *cis*-piperidine was produced as a unique diastereomer albeit in a low yield of 40 % (Table 3, Entry 4). It appears that a compromise had to be found between high yield and good diastereoselectivity and, thus, mixtures of solvents were tested. When the reaction was carried out in a 1:1 mixture of CH_2Cl_2 and CH_3CN, after 17 h at room temp. and 17 h at 50 °C, a 55:45 mixture of *cis*- and *trans*-piperidines was observed, which confirmed the detrimental role of CH_3CN on the diastereoselectivity of the cyclization. Additional heating at 50 °C for 17 h did not improve the ratio (Table 3, Entry 5). A mixture of CH_2Cl_2 with TFE (1:1) delivered the *cis*-piperidine with perfect diastereocontrol and with a slightly improved yield relative to those obtained with CH_2Cl_2 alone (66 % versus 63 %) (Table 3, Entry 6). However, as the increase of the yield was not outstanding, simple experimental conditions were favored and the generality of the reaction was investigated by using either CH_2Cl_2 or CH_3CN.

Table 3. Optimization study for the synthesis of 2,6-disubstituted piperidine **4a**.



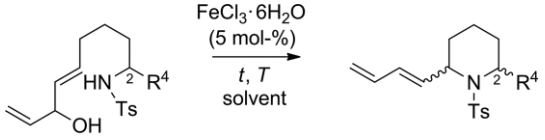
Entry	Solvent	*t*	*T* [°C]	*dr*[a]	**4a** (yield)
1	CH_2Cl_2	17 h	r.t.	96:4	63 %
2	CH_3CN	17 h	r.t.	55:45	nd
3	CH_3CN	17 h + 52 h	r.t. then 50 °C	83:17	84 %
4	TFE	17 h	r.t.	> 95:5	40 %
5	CH_2Cl_2/CH_3CN	17 h + 17 h	r.t. then 50 °C	55:45	65 %
6	CH_2Cl_2/TFE	17 h	r.t.	> 95:5	66 %

[a] *cis*/*trans* ratio determined by using GC/MS analysis.

Various precursors of α-dienyl disubstituted piperidines were treated with $FeCl_3·6H_2O$ (5 mol-%) in CH_2Cl_2 or CH_3CN. The evolution of the diastereomeric ratio was monitored by GC/MS and the reactions were quenched when a constant value was reached. In some cases, heat was required to favor the *cis*/*trans* equilibration and increase the diastereomeric ratio. The presence of a phenyl substituent was tolerated and the corresponding 2,6-disubstituted piperidine was isolated with a satisfying yield of 66 % and an excellent *cis*/*trans* ratio (90:10) (Table 4, Entry 1). In the presence of a methyl group, after 17 h at room temp., a moderate 69:31 *cis*/*trans* ratio was obtained in CH_2Cl_2. The use of heat at 50 °C for 2 h was necessary to reach a good diastereoselectivity (*cis*/*trans* = 94:6; Table 4, Entry 2). Disappointingly, the cyclized product was produced in a moderate 53 % yield. When the same reaction was carried out in CH_3CN, after 17 h at room temp. and 31 h at 50 °C, a moderate diastereomeric ratio was reached (80:20). However, further heating led to decomposition, which prevented the isolation of the expected piperidine (Table 4, Entry 3).

The influence of the *N*-substituent was next investigated. As a nosyl group is generally easier to cleave than a tosyl group, cyclization of **3d** was attempted. In CH_2Cl_2 the reaction yielded

Table 4. Variation of the C2 substituent R^4.



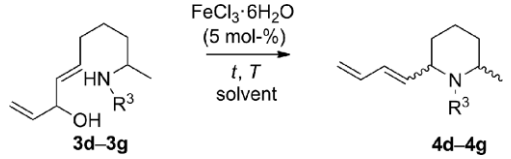
3b–3c 4b–4c

Entry	3	R^4	Solvent	t	T [°C]	dr[a]	4 (yield)
1	**3b**	Ph	CH_2Cl_2	19 h	r.t.	90:10[b]	**4b** (66 %)
2	**3c**	Me	CH_2Cl_2	17 h + 2 h	r.t. then 50 °C	94:6[b]	**4c** (53 %)
3[d]	**3c**	Me	CH_3CN	17 h + 31 h	r.t. then 50 °C	80:20[c]	nd

[a] *cis*/*trans* ratio. [b] Ratio determined by analysis of the crude ^1H NMR spectrum. [c] Ratio determined by analysis of GC/MS. [d] Decomposition was observed.

the piperidine in 70 % yield with moderate diastereocontrol (*cis*/*trans* = 85:15), whereas an equimolar mixture of *cis*- and *trans*-isomers was obtained in CH_3CN even after 22 h at 50 °C (Table 5, Entries 1 and 2). We hypothesized that the nosyl group could interfere with the iron-induced equilibration process upon coordination of the nitro group with the metal catalyst. Carbamates are compatible with the reaction conditions but once again a compromise has to be found between good yield and good diastereoselectivity. In CH_2Cl_2, piperidines **4e** and **4f** were produced in moderate yield (55 and 61 %, respectively) with acceptable diastereomeric ratio (80:20; Table 5, Entries 3, 5, and 6). In contrast, when CH_3CN was used, good yields were obtained (87 and 80 %) together with poor diastereoselectivity (70:30 and 65:35) (Table 5, Entries 4 and 7). The presence of an acetyl group on the nitrogen atom was detrimental to the cyclization as a mixture of products was formed from **3g** in both CH_2Cl_2 and CH_3CN, probably as a result of poor nucleophilicity of the amide moiety (Table 5, Entries 8 and 9).

Table 5. Variation of the *N*-substituent.

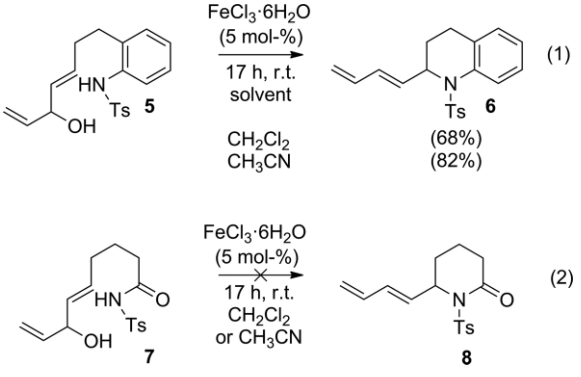


3d–3g 4d–4g

Entry	3	R^3	Solvent	t	T [°C]	dr[a]	4 (yield %)
1	**3d**	Ns	CH_2Cl_2	18 h + 5 h	r.t. then 50 °C	85:15	**4d** (70 %)
2	**3d**	Ns	CH_3CN	18 h + 22 h	r.t. then 50 °C	50:50	**4d** (46 %)
3	**3e**	Boc	CH_2Cl_2	17 h	r.t.	80:20	**4e** (55 %)
4	**3e**	Boc	CH_3CN	24 h	r.t.	70:30	**4e** (87 %)
5	**3f**	CBz	CH_2Cl_2	17 h + 2 h	r.t. then 50 °C	60:40	**4f** (58 %)
6	**3f**	CBz	CH_2Cl_2	17 h + 67 h	r.t. then 50 °C	80:20	**4f** (61 %)
7	**3f**	CBz	CH_3CN	17 h + 52 h	r.t. then 50 °C	65:35	**4f** (80 %)
8[b]	**3g**	Ac	CH_2Cl_2	26 h	r.t.	nd	nd
9[b]	**3g**	Ac	CH_3CN	18 h	r.t.	nd	nd

[a] *cis*/*trans* ratio determined by analysis of the crude ^1H NMR spectrum. [b] Decomposition was observed.

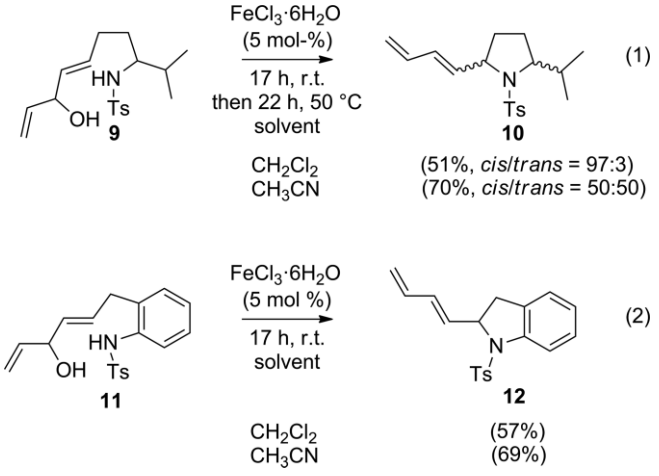
This iron-catalyzed cyclization of amino-dienols was not restricted to the synthesis of piperidines. It was also suitable to access α-dienyl tetrahydroquinoline frameworks as attested by the formation of **6** from **5** in high yield in CH_3CN (Scheme 4, Equation 1). However, the developed conditions did not allow the preparation of six-membered ring lactams because a complex mixture of products was obtained upon treatment of **7** with $FeCl_3$·$6H_2O$ whichever solvent was used. As a result of poor nucleophilicity of the nitrogen atom, the cyclization did not proceed and resulted in the formation of several non-identified by-products (Scheme 4, Equation 2).



Scheme 4. Synthesis of other six-membered ring N-heterocycles.

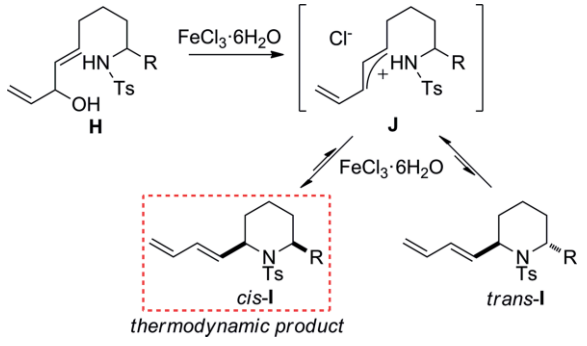
In addition, α-dienyl pyrrolidine **10** was successfully synthesized from the corresponding precursor **9**. Nevertheless, as in the case of 2,6-disubstituted piperidines, we were not able to find conditions to produce both high yield and diastereoselectivity. In CH_2Cl_2, the cyclization proceeded in modest yield (51 %) and great diastereocontrol (*dr* = 97:3), whereas in CH_3CN the five-membered ring was obtained in an improved yield (70 %) but without any diastereoselectivity (Scheme 5, Equation 1). Finally, indoline **12** could be formed by cyclization of **11** (Scheme 5, Equation 2).

Under iron catalysis, the reactivity of bis-allylic alcohols appears similar to the reactivity of mono-allylic alcohols or acetates previously studied for the synthesis of alkenyl piperidines.[26] Thus, based on our observations and previous results, the mechanism depicted in Scheme 6 for the formation of α-dienyl piperidines can be proposed. The iron catalyst may activate the bis-allylic alcohol to provide a carbocation, which could be stabilized by the presence of the diene moiety.[27] Intramolecular nucleophilic attack of the nitrogen atom on the carbocation intermediate may occur at the position that led to the six-membered ring substituted by a conjugated diene. This initial nucleophilic attack may proceed in a non-diastereoselective fashion as confirmed by the low to moderate diastereo-



Scheme 5. Synthesis of five-membered ring N-heterocycles.

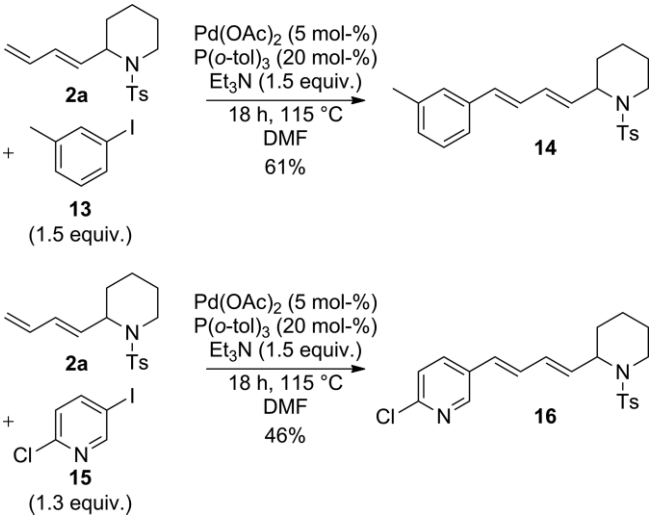
meric ratio obtained after a short reaction time. The evolution of the diastereomeric ratio with time and temperature suggested an iron-induced ring opening/closure of the N-heterocycle to allow a thermodynamic equilibrium to be established. This equilibration may result in the formation of the most stable *cis*-isomer as the major compound. We hypothesized that the low to moderate diastereoselectivities obtained in CH_3CN could result from coordination of the nitrile to the iron center, which decreases its ability to mediate the re-opening of the piperidine.



Scheme 6. Hypothetical mechanism.

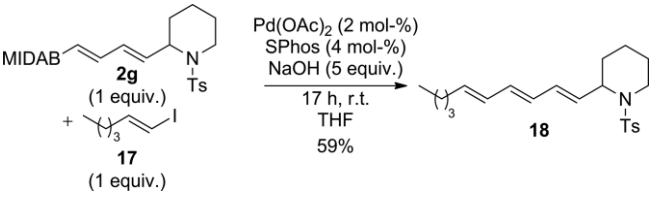
To demonstrate that the method could be an attractive synthetic tool to access functionalized α-dienyl and α-polyenyl N-heterocycles, several transformations were performed on a few cyclized products. The functionalization of the diene moiety was first examined and a Heck coupling was performed on terminal diene **2a**. Treatment of **2a** with aryl iodide **13** under palladium catalysis, in the presence of a base, led to the expected substituted diene in 61 % yield. The reaction was more problematic with heteroaromatic iodide **15** as the Heck product was formed with a low yield of 46 %. We hypothesized that the nitrogen atom of the pyridine may cause the catalyst poisoning in spite of the presence of the C2 chlorine atom that may reduce the Lewis basicity of the pyridine[28] (Scheme 7).

The formation of α-trienyl piperidines was then investigated. The α-dienyl piperidines that incorporated the MIDA vinyl boronate could be engaged in a Suzuki coupling with an alk-



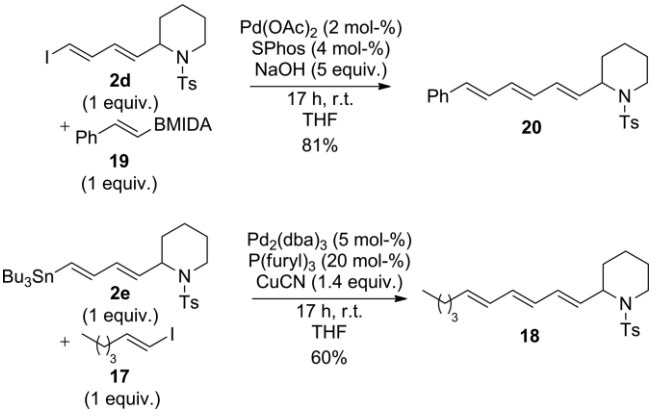
Scheme 7. Heck coupling between **2a** and (hetero)aryl iodides. DMF = dimethylformamide.

enyl iodide. For instance, when **2g**, which results from the cyclization of **1g**, was treated with alkenyl iodide **17** in the presence of $Pd(OAc)_2$, SPhos, and NaOH, expected triene **18** was isolated in a satisfying yield of 59 % (Scheme 8).[29]



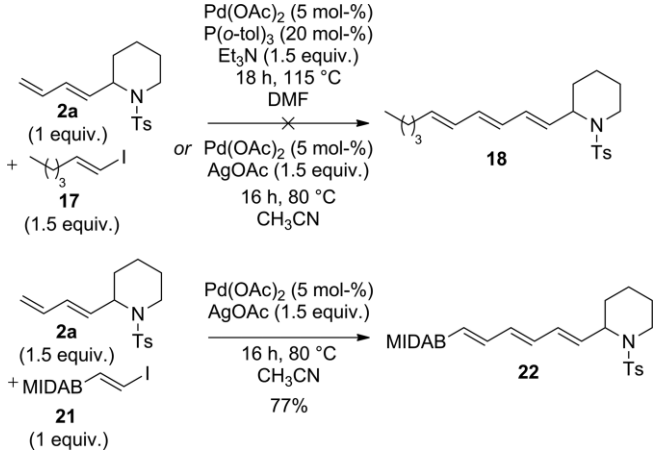
Scheme 8. Suzuki coupling on a BMIDA containing α-dienyl piperidine. THF = tetrahydrofuran.

Piperidines **2d** and **2e**, that feature an alkenyl iodide and an alkenyl stannane, respectively, could also be good partners in metal-catalyzed cross-coupling reactions. A palladium-catalyzed Suzuki coupling between **2d** and alkenyl boronate **19** delivered triene **20** in 81 % yield. When alkenyl stannane **2e** was reacted in a Stille coupling with alkenyl iodide **17**, the corresponding triene was formed efficiently (60 %) (Scheme 9).[30]



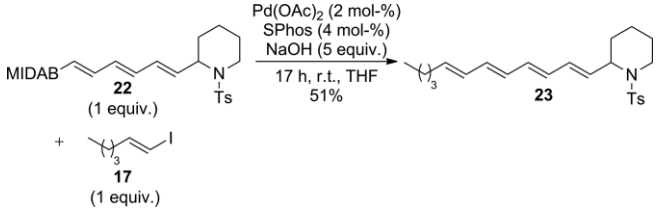
Scheme 9. Access to α-trienyl piperidines by using metal-catalyzed coupling.

The Heck coupling between a terminal diene and an alkenyl iodide is an alternative approach towards the formation of triene frameworks. Disappointingly, the reaction between **2a** and alkenyl iodide **17** only delivered traces of the Heck product under two sets of conditions. However, the use of conditions recently developed in our group allowed the Heck coupling between **2a** and alkenyl iodo MIDA boronate **21** in good yield (77 %) (Scheme 10).[31]



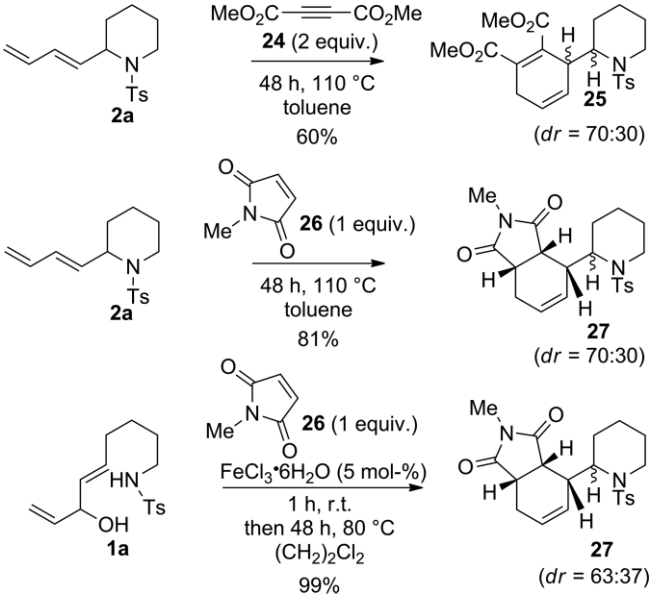
Scheme 10. Heck coupling between **2a** and alkenyl iodides.

Trienyl MIDA boronate **22** is a potent intermediate towards the synthesis of various α-polyenyl piperidines. For example, it could react with alkenyl iodide **17** under palladium catalysis to afford tetraene **23** in moderate yield (Scheme 11).



Scheme 11. Access to an α-tetraenyl piperidine.

By taking advantage of the presence of the diene, Diels–Alder cycloadditions were performed.[32,33] α-Dienyl piperidine **2a** was heated with diethyl but-2-ynedioate to give the corresponding Diels–Alder adduct **25** in a yield of 60 %.[34] An excess of the alkyne partner as well as a prolonged reaction time at 110 °C were necessary to reach complete conversion of the diene. The reaction between **2a** and *N*-methylmaleimide proceeded smoothly to deliver tricyclic compound **27** in 81 % yield.[35] It is worth nothing that a one-pot process that includes the iron-catalyzed cyclization and the Diels–Alder reaction could be developed for this transformation. When dienic amino alcohol **1a** was treated with $FeCl_3 \cdot 6H_2O$ in the presence of *N*-methylmaleimide in $(CH_2)_2Cl_2$ for 1 h at room temp. and 48 h at 80 °C, a cascade reaction took place and desired product **27** was isolated in quantitative yield (Scheme 12).[36]



Scheme 12. Diels–Alder reactions.

Conclusions

An iron-catalyzed cyclization reaction to access α-dienyl-substituted N-heterocycles has been developed. The method displays several advantages, such as low-toxicity, low-cost, and atom economy, with water being the only waste product. A range of mono- and disubstituted N-heterocycles that incorporate a dienic substituent were prepared with moderate to excellent yield and diastereoselectivity. The synthetic utility of the method was demonstrated by the formation of several α-polyenyl piperidines from α-dienyl piperidines by using various metal-catalyzed coupling reactions. In addition, a one-pot cyclization/Diels–Alder process was successfully performed and delivered an original tricyclic scaffold.

Experimental Section

General Remarks: All reactions were carried out under an argon atmosphere unless otherwise noted. THF, Et_2O, CH_2Cl_2, and toluene were dried by using a MBraun SPS800 purificator. $FeCl_3 \cdot 6H_2O$ was purchased from ACROS as 96 % pure. All Grignard reagents for which the preparation is not described were purchased from Sigma Aldrich and used as simple Grignard reagents (RMgX without LiCl). All other commercially available chemicals were used as received without further purification. TLC was performed with silica gel plates visualized either with a UV lamp (254 nm) or by using a staining solution (p-anisaldehyde or $KMnO_4$) followed by heating. Purification was performed with silica gel (Merck-Kieselgel 60, 230–400). NMR spectra were recorded with a Bruker AVANCE 400. ^1H NMR spectra were recorded at 400 MHz and proton chemical shifts are reported relative to residual solvent peak [$CDCl_3$ at δ = 7.26 ppm; $(CD_3)_2CO$ at δ = 2.05 ppm; $(CD_3)_2SO$ at δ = 2.50 ppm]. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextuplet, hept = heptuplet, oct = octuplet, m = multiplet or overlap of non-equivalent resonances), integration. ^{13}C NMR spectra were recorded at 100 MHz and carbon chemical shifts are reported relative to residual solvent peaks [$CDCl_3$ at δ = 77.16 ppm; $(CD_3)_2CO$

at 29.84 or 206.26 ppm; $(CD_3)_2SO$ at δ = 39.52 ppm]. Data are reported as follows: chemical shift in ppm, coupling constants. Infrared (IR) spectra were recorded with a Bruker TENSORTM 27 (IRFT). Mass spectra with Electronic Impact (MS-EI) were recorded with a Shimadzu GC–MS-QP2010S Gas Chromatograph/Mass Spectrometer. High-resolution mass spectra (HRMS) were realized at the Laboratoire de Spectrométrie de Masse SM3E de l'Université Pierre et Marie Curie, Paris. Melting points were determined with a Kofler bench or a Büchi melting point apparatus in open capillaries.

Supporting Information (see footnote on the first page of this article): Further details can be found in supporting information.

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Keywords: Earth-abundant metals · Iron · Synthetic methods · Piperidine · Nitrogen heterocycles · Cyclization

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[18] See ref.[10] and ref.[11a]

[19] See the supporting information for the evaluation of some other Lewis acids in the same transformation.

[20] By working at 0 °C the reaction slowed and, after 10 min, the cyclized product was isolated in a low yield of 39 %.

[21] The cyclization also proceeded smoothly in TFE (96 %,) whereas a mixture of products was produced in hexafluoroisopropanol.

[22] The use of TFE proved really beneficial and allowed the formation of **2c** in 94 % yield.

[23] See the experimental details for the synthesis of **1g**.

[24] Compound **1g** was not soluble in CH_2Cl_2.

[25] When **3a** was treated with $InCl_3$ (5 mol-%) in CH_2Cl_2 at room temp., after 17 h, a *cis*/*trans* ratio of 60:40 was observed, which emphasizes the crucial role of the iron catalyst in the diastereoselectivity of the cyclization through its ability to induce an epimerization process.

[26] Alkenyl piperidines were obtained from mono-allylic alcohols or acetates at room temp. in CH_2Cl_2 in the presence of $FeCl_3{\cdot}6H_2O$ (5–10 mol-%) in 61–99 % yield with a *dr* > 90:10 (see ref.[17]). The lower yields obtained for the formation of α-dienyl piperidines than for α-alkenyl piperidines may result from problems of stability of the diene under the reaction conditions.

[27] During the synthesis of alkenyl piperidines, the formation of a cationic intermediate was confirmed by using an optically active mono allylic acetate. A racemic piperidine was isolated and the absence of chirality transfer supported the hypothetical carbocationic intermediate (see ref.[17a]).

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[34] The relative configuration of the major diastereomer has not been determined.

[35] The *cis* relationship between the three protons on the tertiary carbon atoms of the cyclohexene was proposed by assuming an *endo* approach. The relative configuration of the stereocenter at C2 of the piperidine in the major diastereomer has not been determined.

[36] This result may confirm that the moderate yields obtained for the cyclization of *bis*-allylic alcohols may result from a stability issue of the resulting diene moiety under the reaction conditions. In this tandem process, the diene is immediately trapped by the dienophile and a quantitative yield is obtained for the formation of the Diels–Alder adduct.

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