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Catalytic imino-Diels–Alder reactions of 2-aminodienes: a simple entry into structurally diverse pipecolic acid derivatives

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Abstract—The stereoselective synthesis of 4-aminotetrahydropyridines by cycloaddition reaction of 2-amino-1,3-butadienes with *N*-alkyl and *N*-aryliminoesters in the presence of a catalytic amount of a Lewis acid is described. The reaction proceeds with differently substituted 2-aminodienes, giving rise to structurally diverse pipecolic acid derivatives. © 2002 Published by Elsevier Science Ltd.

The piperidine ring is a very important structural motif, which is present in a large variety of natural alkaloids and pharmaceuticals. A powerful approach to the synthesis of this class of heterocycles is the imino-Diels–Alder reaction, which involves an imine derivative and an activated carbodiene, usually in the presence of a Lewis acid as catalyst.[1] The imino-Diels–Alder reaction has been extensively studied, and in the literature can be found examples of the participation of activated, non-activated, and functionalized imines. Moreover, asymmetric versions of the reaction have led to chiral six membered ring heterocycles by using chiral auxiliaries attached either to the imine or the diene.[2] Very recently, excellent methodologies for the catalytic asymmetric cycloaddition have been disclosed.[3]

However, in spite of the considerable amount of work dedicated to the imino-Diels–Alder reaction, and with the exception of some particular contributions,[4] most of the examples are restricted to a limited number of highly activated dienes, such as 1-alkoxy-3-trialkylsilyloxydiene 'Danishefsky's diene' and related systems, and cyclic dienes like cyclopentadiene. In particular, Danishefsky's diene has concentrated most of the efforts in the development of asymmetric catalytic imino-Diels–Alder reactions.

Therefore, in order to develop convergent approaches to structurally diverse piperidines, it seems desirable to discover new types of 1,3-butadienes which can participate in imino-Diels–Alder reactions as efficiently as the 1-alkoxy-3-trialkylsilyloxy systems. In this context, several years ago, we described the cycloaddition of 2-amino-1,3-butadienes with non-activated imines, which gives rise to 4-aminotetrahydropyridines with good yields and diastereoselectivities.[5] Moreover, when the aminodiene carries a chiral amine, the reaction proceeds with very high facial diastereoselectivity yielding, after acidic hydrolysis of the resulting enamine, 4-piperidones with very high enantiomeric excesses (Fig. 1).[6] This type of functionalized piperidine derivatives have proven to be interesting intermediates in the synthesis unnatural α-amino acids and of natural alkaloids.[7]

Nevertheless, this methodology suffered from some limitations: the requirement of a particular substitution pattern ($-CH_2OR$) in the position 4 of the diene and the need of an stoichiometric amount of the Lewis acid used ($ZnCl_2$), which would not allow for the development of a catalytic asymmetric version of the reaction.

In the light of the development of very efficient Lewis acids for activation of imines, mainly directed to catalytic asymmetric synthesis, which have appeared in the recent years, we decided to revisit the imino-Diels–Alder reaction of 2-aminodienes with imines, oriented towards the development of a process more general in

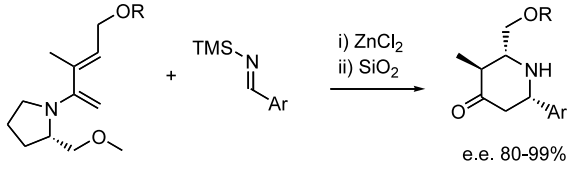

Figure 1. Imino-Diels–Alder reaction of chiral 2-aminodienes.

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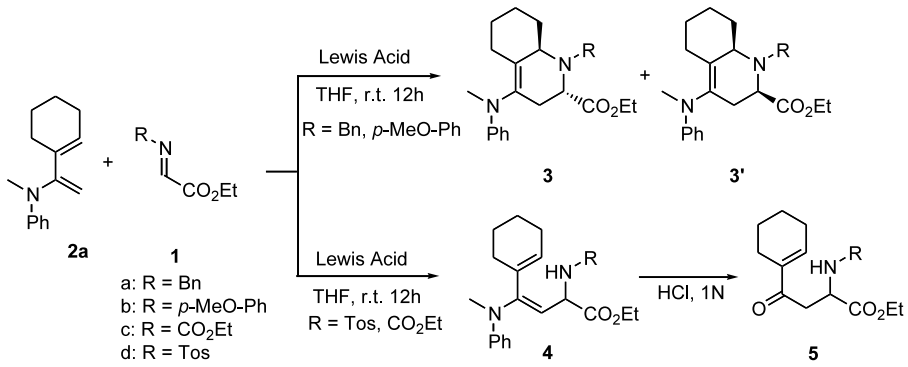


Scheme 1. Reactions of 2-aminodiene **2a** with differently substituted iminoesters.

Table 1. Influence of the catalyst in the synthesis of cycloadducts **3** and **3′**

Compound	R	Lewis acid (% mol)	Solvent	Ratio **3**:**3′**[a]	Yield (%)[b]
aa	Benzyl	$CuClO_4$ (10%mol)	THF	1:4	50
aa	Benzyl	$CuClO_4$ (10%mol)	CH_2Cl_2	1:4	42
aa	Benzyl	$CuClO_4$ (20%mol)	CH_2Cl_2	1:4	46
aa	Benzyl	$CuClO_4$ (20%mol)	THF	1:7	66
aa	Benzyl	$Cu(OTf)_2$ (20%mol)	THF	10:1	63
aa	Benzyl	$Yb(OTf)_3$ (20%mol)	THF	19:1	72
ab	*p*-MeO-Ph	$CuClO_4$ (20%mol)	THF	4:1	83
ab	*p*-MeO-Ph	$Cu(OTf)_2$ (20%mol)	THF	4:1	74
ab	*p*-MeO-Ph	$Yb(OTf)_3$ (20%mol)	THF	4.5:1	77

[a] Determined by ^{1}H NMR.
[b] After chromatographic purification.

the structure of the aminodiene and catalytic with respect to the Lewis acid. In this paper we would like to present our initial results in this field.

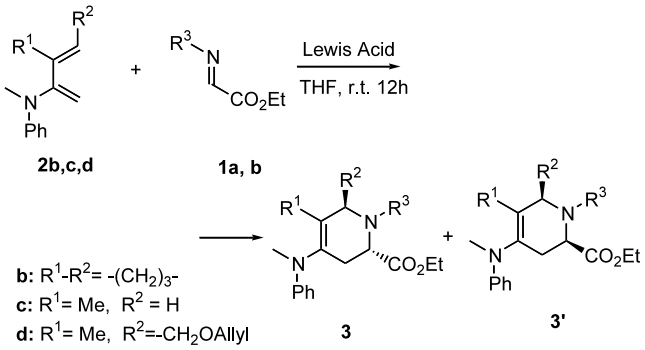
We chose for our study iminoesters **1**, very attractive substrates for the imino-Diels–Alder reaction, which furnish, after [4+2] cycloaddition, derivatives of the naturally occurring α-amino acid pipecolic acid, and which have been employed successfully in catalytic asymmetric reactions with Danishefsky's diene.[3b,c] The iminoesters were reacted with 2-amino-1,3-butadiene **2a**. The selection of this particular system was motivated for various reasons: the presence of an additional substituent in position 4 of the diene which allows for the study of the diastereoselectivity of the process, and the particular synthetic interest of the resulting bicyclic systems, not easily accessible by the cycloaddition of Danishefsky's type of dienes.

With regard to the Lewis acid catalysts, we used some compounds which have been shown to activate imines in a catalytic fashion in cycloaddition[3] and Mannich-type reactions:[8,9] $CuClO_4$, $Cu(OTf)_2$ and $Yb(OTf)_3$.

The reactions were carried out employing 10 to 20% mol of the Lewis acid. Under the conditions described, the reactions with *N*-alkyl substituted imines **1a**, and *N*-aryl substituted imines **1b**, afforded the expected [4+2] diastereomeric cycloadducts **3** and **3′**, as racemic mixtures, and with yields and diastereoselectivities ranging from moderate to good depending on the nature of the substituent on the nitrogen of the imine. It was observed that the best results were achieved when 20% mol of the catalysts were employed (Scheme 1 and Table 1).

The diastereoselectivity of the cycloaddition is influenced by several factors, mainly the substitution on the nitrogen of the imine and the Lewis acid used. Higher diastereoselectivities were observed for the alkyl substituted *N*-benzylimine **1a** than for the aryl substituted *N*-*p*-OMe imine **1b**. Moreover, for the *N*-benzyl substituted imine, the variation of the Lewis acid determines the stereochemical course of the cycloaddition: while $CuClO_4$ induces the formation of 4-tetrahydropyridine **3′aa**, $Cu(OTf)_2$ and $Yb(OTf)_3$ promote the formation of diastereomer **3aa**. This different behavior was not observed for the *N*-aromatic substituted imine **1b**, and in all cases isomer **3ab** was the major one. Regarding the Lewis acid, best yields and diastereoselectivities were obtained when the reactions were carried out with $Yb(OTf)_3$. It is interesting to note that isomer **3′** features the substituents in positions 2 and 6 in a *cis* arrangement, which is in agreement with an *endo* approach of the carboxylic group in the transition state of a formal concerted [4+2] cycloaddition, while diastereomer **3** would come from an *exo* approach of the carboxylate.[†] Nevertheless, up to now, we have no

[†] The relative arrangement of the stereogenic centers was determined by analysis of the ^{1}H NMR spectra and NOESY experiments on 4-aminotetrahydropyridines **3** and **3′** and further confirmed upon hydrolysis of the enamine moiety (see below for the discussion of the stereochemistry of **6aa**).

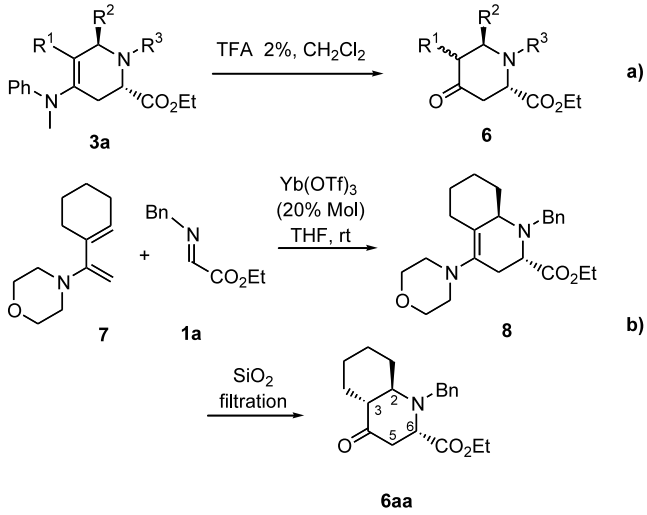


Scheme 2. Synthesis of 4-aminotetrahydropyridines **3** and **3′**.

evidence to decide between a concerted [4+2] cycloaddition or a stepwise reaction, and additional experiments are required in order to shed some light onto the mechanism of the reaction.

Interestingly, a completely different result was obtained when activated iminoesters (R = -Tos, $-CO_2Et$) were employed. In these cases the reaction did not afford the cycloadducts but the Mannich-type addition products **4**, coming from the electrophilic attack of the enamine to the strong nucleophilic carbon of the *N*-acylimine. The open chain compounds were characterized as the ketoaminoesters **5** after hydrolysis of the imine functionality. Further experiments revealed that this Mannich-type reaction is very fast and proceeds even in the absence of the Lewis acid.

The study of the cycloaddition reaction was then expanded to other 2-aminodienes **2** with different substitution patterns (Scheme 2 and Table 2). As expected, the reactions proceeded to afford the corresponding racemic 4-aminotetrahydropyridine derivatives. Again, the best yields and selectivities were obtained with $Yb(OTf)_3$ for the reactions with the *N*-benzylimine. Unfortunately, the reactions with the *N*-arylimine showed no diastereoselectivity at all under any of the conditions examined.



Scheme 3. Hydrolysis of 4-aminotetrahydropyridines **3**. Synthesis of 4-piperidones **6**.

Moreover, the reverse diastereoselectivities obtained for the reaction of diene **2a** with $CuClO_4$ were not observed for dienes **2b** and **2d**, and in all the examples isomer **3**, which features the substituents in positions 2 and 6 in a *trans* arrangement, was the major isomer formed.‡ The influence of the substituents on the diene is noteworthy: in particular, for diene **2c** (R² = H) the 4-aminotetrahydropyridines **3** are obtained with nearly quantitative yield, probably due to the minor steric hindrance of this particular system.

This type of 4-aminotetrahydropyridines are stable compounds under aqueous neutral conditions and in most of the cases can even be purified by column chromatography with silica gel without hydrolysis of the enamine moiety or ring opening. Hydrolysis of the enamine can be achieved by treatment with 2% TFA in methylene chloride to give rise to the corresponding ketones. However, the hydrolytic process is not always stereoselective, and in some examples a mixture of the

Table 2. The prepared 4-aminotetrahydropyridines **3** and **3′**

Compound	R^1	R^2	R^3	Lewis acid (20 mol%)	Ratio **3**:**3′**[a]	Yield (%)[b]
ba	$-(CH_2)_3-$		Benzyl	$CuClO_4$	3:1	40
ba	$-(CH_2)_3-$		Benzyl	$Yb(OTf)_3$	<20:1	55
ba	$-(CH_2)_3-$		Benzyl	$Cu(OTf)_3$	<20:1	48
bb	$-(CH_2)_3-$		*p*-MeO-Ph	$CuClO_4$	1:1	64
bb	$-(CH_2)_3-$		*p*-MeO-Ph	$Cu(OTf)_3$	1:1	64
bb	$-(CH_2)_3-$		*p*-MeO-Ph	$Yb(OTf)_3$	1:1	64
ca	Me	H	Benzyl	$Yb(OTf)_3$	–	89
cb	Me	H	*p*-MeO-Ph	$Yb(OTf)_3$	–	90
da	Me	$CH_2OAllyl$	Benzyl	$CuClO_4$	3.5:1	50
da	Me	$CH_2OAllyl$	Benzyl	$Yb(OTf)_3$	4:1	55

[a] Determined by ^1H NMR.
[b] After chromatographic purification.

‡ The arrangement of the stereogenic centers in compounds **3ba**, **3bb** and **3da** was deduced from the analysis of the ^1H NMR spectra of the corresponding ketones **6** (see below for **6aa**), because due to the flat structure of compounds **3**, their ^1H NMR and NOESY experiments did not lead to an unambiguous assignment.

two possible diastereomers **6** and **6′** is obtained in variable rates as depicted in Scheme 3(a).

Interestingly, changing the amino substituent of the diene plays an important role in the outcome of the reaction sequence. Thus, when the cycloaddition with imine **1a** was carried out with the morpholine substituted diene **7**, under the same reaction conditions, the expected 4-aminotetrahydropyridine **8** was formed as a major diastereomer, as determined by the analysis of the ^{1}H and ^{13}C NMR spectra of the reaction crude. However, this time, filtration through a short chromatographic column afforded the bicyclic ketone **6aa** as a single diastereomer in 60% overall yield (Scheme 3b).[§]

As expected, the more electron-donor ability of morpholine compared to an *N*-aromatic substituted amine increases the enaminic character of the double bond, becoming more unstable under acidic conditions. Moreover, the hydrolysis takes place with very high diastereoselectivity. Therefore, it seems that *N*-aryl substituted dienes are appropriate for the synthesis of 4-aminotetrahydropyridines, while the preparation of 4-piperidones can be achieved more conveniently with *N*-alkyl substituted (morpholine) dienes.

We have therefore described a novel catalytic [4+2] cycloaddition of 2-aminodienes with iminoesters which provides a very convergent method for the synthesis of 4-aminotetrahydropyridines and 4-piperidones with high diastereoselectivities. The reaction can be carried out with a variety of dienes bearing different types of substituents, opening the door to the synthesis of structurally diverse piperidine derivatives. In particular, the easy availability of cyclopentene- and cyclohexene-derived dienes may allow for the very direct preparation of bicyclic alkaloid scaffolds. Our current efforts are oriented to the development of an enantioselective version of the reaction which we plan to achieve by either incorporating chiral ligands to the Lewis acid or chiral auxiliaries attached to the dienes or the imines. Progress in this field will soon be reported.

Typical experimental procedure for the synthesis of 4-aminotetrahydropyridines 3

The Lewis acid (0.2 mmol) was placed under N_2 into a flame-dried Schlenk tube and was dried for 1 h under vacuum. Freshly distilled anhydrous solvent (10 ml) was added with a syringe under N_2 and the resulting solution was stirred for 30 min at room temperature. The solution was treated with imino ester **1** (1 mmol) and stirred for 5 min. Finally, the diene **2** (1.1 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 12 h, quenched with $NaHCO_3$ sat. aqueous solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product purified by flash chromatography (SiO_2, EtOAc:hexanes 1:9). Yellow oil. R_f values (SiO_2, EtOAc:hexanes 1:9): **3′aa**, 0.25; **3aa**, 0.37.

Selected spectroscopic data for compound 3aa

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13–1.20 (3H, t, $J=7.1$ Hz), 1.22–1.47 (2H, m), 1.63–1.75 (4H, m), 2.14–2.28 (1H, m), 2.37–2.45 (1H, m), 2.7 (1H, m), 2.9 (1H, m), 3.01 (3H, s), 3.8 (3H, m), 4.07 (2H, c, $J=7.1$ Hz), 4.35–4.39 (2H, dd, $J=6.4$ Hz, 2.6 Hz), 6.65–7.35 (9H, m) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1 (CH_3), 24.6 (CH_2), 26.9 (CH_2), 27.7 (CH_2), 29.4 (CH_2), 33.2 (CH_2), 36.8 (CH_3), 55.2 (CH_3), 56.2 (CH), 60.2 (CH), 61.3 (CH), 112.1 (CH), 113.9 (CH), 116.3 (CH), 128.9 (CH), 129.8 (C), 136.1 (C), 142.3 (C), 147.7 (C), 154.7 (C), 172.8 (C=O) ppm.

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[§] The relative arrangement of the stereogenic centers of **6aa** was determined by the analysis of the ^{1}H spectra: the large coupling constant between H_2 and H_3 (10 Hz) establishes the axial disposition of both protons, while the presence of two small couplings between H_6 and H_{5a} and H_{5b} (6.8 and 1.9 Hz, respectively) points to an equatorial disposition of H_6. NOESY experiments on **6aa** agree completely this assignment.

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