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Scandium(III)-Zeolites as New Heterogeneous Catalysts for Imino-Diels–Alder Reactions

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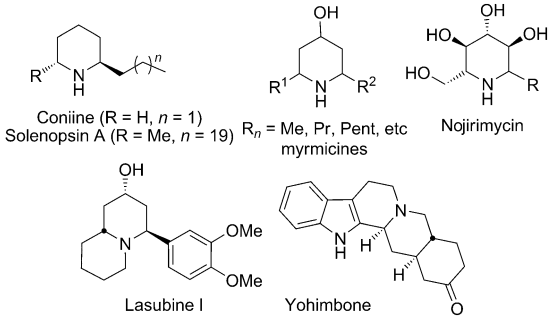
Abstract: This study demonstrates the first zeolite-catalyzed synthesis of piperidine derivatives, including peptidomimetics and indoloquinolizidine alkaloids. The approach developed utilizes a highly effective one-pot reaction cascade, through imine formation and imino-Diels–Alder reactions, promoted by scandium-loaded zeolites as a heterogeneous catalyst. The methodology described benefits from very low catalyst loadings (≤ 5 mol % of Sc^{III}), commercially and readily available starting materials, and mild reaction conditions. Furthermore, the Sc^{III}-zeolite catalyst can be readily reused more than 10 times without any loss in efficiency.

Keywords: heterogeneous catalysis · imine · peptidomimetics · piperidine · scandium · zeolites

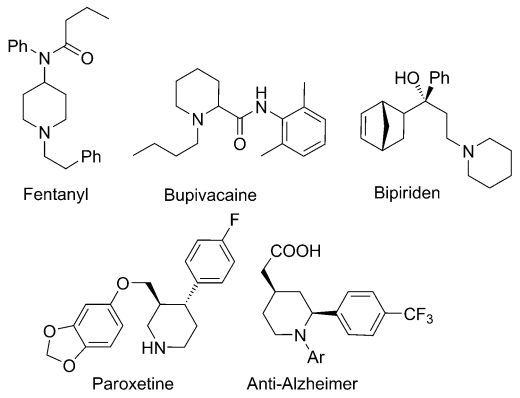
Introduction

Piperidine derivatives: Piperidine heterocycles represent a large important class of natural products from the alkaloid family.[1] Piperidine alkaloids are usually found in plants,[2] and they can exhibit very simple structures (such as coniine), up to more complex structures (such as quinolizidine and indolic alkaloids, for example, lasubine and yohimbine-type alkaloids), through sugar-like nojirimycine and related compounds (Scheme 1). They can also be found in other organisms such as dendrobatid frogs,[3] myrmicine ants, and other insects,[4] although they can be connected to plant alkaloids through ecological relationships (Scheme 1).[5] Piperidine alkaloids often have toxic or deterrent activity as illustrated by solenopsin A, one of the active components of fire-ant venom,[6] or by coniine, from the plant *Conium maculatum*, which has a mammalian LD_{50} of less than 1 mg kg^{-1} and is also the insect-paralyzing component of a pitcher plant, which is active at the nanogram level.[7]



Scheme 1. Selected examples of piperidine natural products.

Furthermore, piperidine probably is the most common heterocycle occurring in drugs,[8] not only as a scaffold but also contributing to a wide range of bioactivities, as represented by, for example, the antidepressant paroxetine, the anti-parkinsonian agent biperiden, the analgesic fentanyl or the anaesthetic bupivacaine, or the recently patented anti-Alzheimer series of compounds (Scheme 2).[9]



Scheme 2. Selected examples of drugs containing the piperidine motif.

Previous efforts and challenges: With such diversity of structures and applications, numerous synthetic approaches towards piperidine derivatives have been developed.[10] Among them, the [4+2] cycloaddition between imines and some dienes has long been recognized as one of the most convenient and rapid synthetic methods.[11] Such so-called imino-Diels–Alder reactions have been reported with various soft Lewis acid catalysts, such as zinc,[12] zirconium,[13] bismuth[14]and lanthanide[15], and more recently niobium

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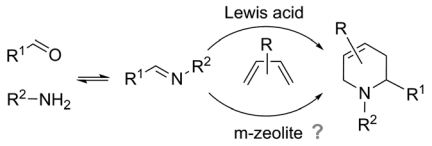


Scheme 3. Known and possible routes to the piperidine motif.

salts[16] (Scheme 3, top). Brønsted acids also proved efficient catalysts for this transformation.[17] Despite the interest in such reactions, heterogeneous reusable catalysts have so far never been used for such applications.[18]

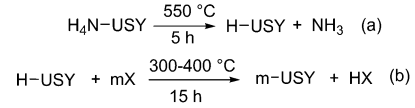
Due to our interest in the latter aspect, and based on our precedents with Cu- and Sc-zeolites,[19,20] we thus wondered if such metal-loaded zeolites could catalyze imino-Diels–Alder reactions (Scheme 3, bottom). Zeolites with their acidic aluminosilicate framework act as Brønsted acids in various reactions.[21] Depending on the nature of the metal, metal ions loaded into zeolites could still act as a Lewis acid. Therefore, metal-loaded zeolites should combine both types of activation, but as solids, they are thus easy to handle and recover. However, an aldehyde, an amine, and a diene must encounter each other within a zeolite pore in order to react. On the other hand, imine formation and stability, as well as diene stability, could be a problem in the presence of zeolites, which are acidic by nature. The fact that Cu^{I}-zeolites could catalyze the formation of propargyl amines from aldehydes, amines, and terminal alkynes[19d] strongly suggests the feasibility of metal-zeolite-catalyzed imino-Diels–Alder reactions.

We report here our results in this area, revealing the first metal-zeolite-catalyzed cycloaddition of imines with dienes and its application to the synthesis of peptide mimics and piperidinoindole alkaloid analogues.

Results and Discussion

Imines, being more or less stable and easily hydrolyzed to their starting components, that is, aldehyde and amine, are usually produced and used in situ, despite the release of water due to their formation, which may be a problem for the next step. In this work, we compared both routes when possible, through either a one- or two-pot process, starting either from aldehyde **1** and amine **2** or from the pre-formed imine **3**.

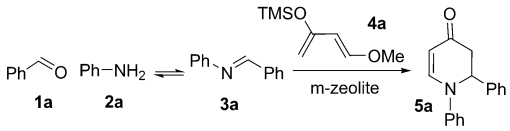
Catalyst and conditions: The commercially available Ultrastable Y (USY) was selected due to its large pores, which are able to accommodate several molecules together as required for imine formation and for Diels–Alder type reactions. USY, modified or not, was also the most efficient zeolite for other reactions.[19,20] The commercial ammonium USY was thus converted to the corresponding copper or scandium-doped USY in two steps with salt sublimation, as already reported (Scheme 4a).[19,20] The amount of salts was calculated to replace 5–10% of the acidic sites of USY, leading to zeolites loaded with the corresponding amount of metallic ions. All these modified zeolites were fully characterized.[22]



Scheme 4. Metal-loaded zeolite synthesis.

With these metal-loaded zeolites as catalysts (5% mol of metal ion), the behavior of the stable imine **3a**, either in situ or already formed from the corresponding benzaldehyde **1a** and aniline **2a**, was examined in the presence of the electron-rich Danishefsky diene[23] **4a** (Table 1).

Table 1. Catalyst and solvent screening.



Entry[a]	Catalyst	Solvent	Time [h]	Yield of **5a** [%][b]
1	None	CH_2Cl_2[c]	72	0
2	H-USY	CH_2Cl_2[c]	24	0–30
3	Cu^{I}-USY	CH_2Cl_2[c]	24	traces
4	Cu^{II}-USY	CH_2Cl_2[c]	24	0
5	Sc^{III}-USY	PhMe	20	0
6	Sc^{III}-USY	CH_2Cl_2	20	0
7	Sc^{III}-USY	THF	20	20
8	Sc^{III}-USY	MeCN	16	48
9	Sc^{III}-USY	MeOH	16	57
10[d]	Sc^{III}-USY	MeCN	1	99
11[d]	Sc^{III}-USY	MeOH	2	57

[a] Reaction performed at room temperature on 0.5 mmol in the presence of 5 mol% of cat. [b] Yields of isolated and purified product; the imine accounted for the mass balance. [c] Other solvents have also been screened, including acetonitrile. [d] Starting from the pre-formed imine **3a**.

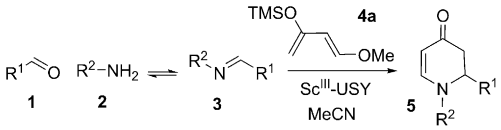
Control experiments showed that no reaction took place without catalyst (Table 1, entry 1), whereas the native H-USY exhibited no or a poor catalytic activity depending on the solvent (Table 1, entry 2). It is interesting to note that the recovery of the Danishefsky diene was possible for a short reaction time (<3 h) but not after a longer reaction time, since it underwent gradual hydrolysis. These results revealed some stability of such dienes despite the acidic zeolitic medium. Both Cu^{I}- and Cu^{II}-USY were not as effective as catalysts; almost no transformation was observed at room temperature resulting in the recovery of the starting materials and the corresponding imine (Table 1, entries 3–4). Nevertheless, with Cu^{I}-USY as catalyst, traces of adduct could be detected after prolonged reaction time (Table 1, entry 3 vs. 4). Rewardingly, Sc^{III}-USY promoted the formation of the expected and known[12] dehydropiperidinone adduct **5a**, but the transformation efficiency proved very dependent on the solvent nature (Table 1, entries 5–11). In this reaction, the more polar the solvent, the better the transformation. Acetonitrile was the more efficient solvent, especially with pre-formed imine, quantitatively giving the dehydropiperidi-

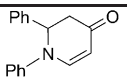
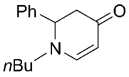
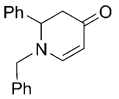
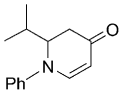
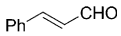
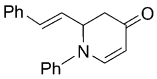
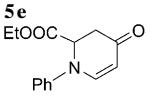
none **5a** (Table 1, entry 10). Although it should have affected the imine formation, methanol unexpectedly gave reasonable amounts of adduct, with the use of either protocol, that is, with in situ or pre-formed imine (Table 1, entries 9 and 11).

Scandium ions, despite their dispersion into zeolites, are thus clearly available to organic moieties and are able to promote imino-Diels–Alder reaction. Even at low loading, Sc^{III}-USY zeolite performs as a very active catalyst for the imino-Diels–Alder reaction.

Catalyst recycling: The recovery and recyclability of this new heterogeneous catalyst for imino-Diels–Alder reaction was evaluated with the same reaction. After the reaction, the Sc^{III}-USY catalyst was recovered through filtration over a nylon membrane. After washing and drying under vacuum at room temperature for 30 minutes, the catalyst was re-engaged in the next run. This procedure was applied at each run, and the catalyst was still highly active for up to ten times (at least),[24] without a noticeable decrease in activity (Figure 1).

Table 2. Scope of the imine component.



Entry[a]	Aldehyde	Amine	T [°C]	t [h]	Yield [%][b]	Adduct
		$PhNH_2$				
1	**1a**	**2a**	20	18	48	**5a**
2[c]	**1a**	**2a**	20	1	99	**5a**
		nBuNH$_2$				
3	**1a**	**2b**	60	18	traces	–
						
4[c]	**1a**	**2b**	20	18	34	**5b**
		tBuNH$_2$				
5	**1a**	**2c**	60	18	0	–
6[c]	**1a**	**2c**	60	18	0	
						
7	**1a**	**2d**	60	18	42	**5c**
8[c]	**1a**	**2d**	20	18	48	**5c**
		$PhNH_2$				
9	**1b**	**2a**	60	18	47	**5d**
10[c]	**1b**	**2a**	20	5	51	**5d**
						
11	**1c**	**2a**	20	18	12	**5e**
12[c]	**1c**	**2a**	20	7	85	**5e**
	EtOOC–CHO					
13	**1d**	**2a**	20	18	82	**5f**

[a] Reaction performed on a 0.5 mmol scale in the presence of 5% of cat. [b] Yields of isolated and purified product; the imine accounted for the mass balance. [c] Starting from the pre-formed imine **3a**.

Scope: To look at the potential and possible limitations of this new heterogeneous imino-Diels–Alder reaction, various commercially available aldehydes and amines were submitted to the Danishefsky diene **4a** under the conditions set above (Table 2). As shown above, aryl amines (such as aniline), and aryl carbaldehyde (such as benzaldehyde), readily reacted in the presence of catalytic amounts of Sc-zeolite and led to the corresponding adduct in modest to good yields (Table 2, e.g., entry 1), but quantitatively if the corresponding imine was pre-formed (entry 2). In contrast, alkylamines gave variable results, depending on the amine structure (Table 2, entries 3–10). Simple primary alkylamines almost did not react, even upon heating (Table 2, entry 3 vs. 1), but pre-forming the imine again helped although the yield of the isolated corresponding adduct remained modest (entry 4 vs. 3). The less basic benzylamine proved more reactive than primary alkylamines, and the one-pot reaction already gave reasonable yield of the expected adduct, whereas pre-forming the imine only slightly increased yields (Table 2, entry 7 vs. 3, entry 8 vs. 4). The bulky *tert*-butylamine did not react regardless of the protocol used (Table 2, entries 5,6).

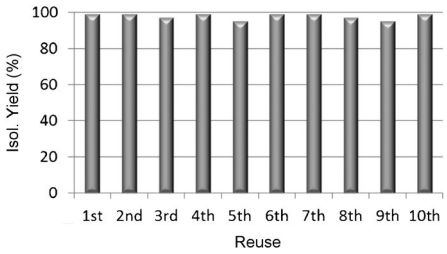


Figure 1. Recycling: Efficiency of recycled Sc^{III}-USY catalyst in the imino Diels–Alder reaction.

Although enamine formation could have been a problem, isobutyraldehyde readily reacted with aniline at room temperature; however, a higher reaction rate was achieved

upon heating. The expected adduct was isolated with reasonable yields, very similar to those observed with benzaldehyde (Table 2, entry 9 vs. 1). Pre-forming the imine only slightly improved the cycloaddition efficiency (Table 2, entry 10 vs. 9).

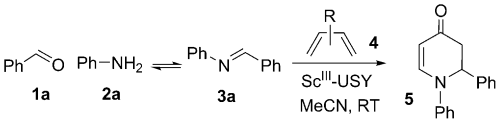
Conjugated aldehydes proved to be also reactive. Cinnamaldehyde gave the expected adduct, albeit the one-pot process was rather slow, even upon heating. Under these reaction conditions, some decomposition occurred and the isolated product yield was thus lower (Table 2, entry 11). With the imine pre-formed, the reaction was faster, even at room temperature, giving high yield of the corresponding adduct upon isolation (Table 2, entry 12). Glyoxylate derivatives proved to be the most reactive among the screened aldehydes. With aniline at room temperature, it gave the corresponding adduct in a high yield (Table 2, entry 13).

In another set of experiments, the nature and the role of the diene were investigated (Table 3). Simple dienes such as methylbutadiene (isoprene) or 2,3-dimethylbutadiene did not react, whereas the more electron-rich Danishefsky diene **4a** readily reacted at room temperature and the Diels–Alder type adduct **5a** was isolated in good to quantitative yields depending on the conditions (Table 3, entry 1 and 2 vs. 3 and 4). The electronic density of the diene may not be the sole factor in this dramatic difference. Diene *S-cis* conformation is obviously required for Diels–Alder cycloaddition, which is less present in (di)methylbutadiene than in the Danishefsky diene.[25]

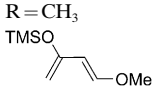
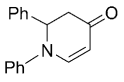
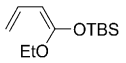
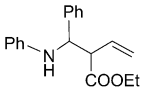
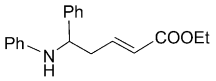
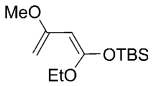
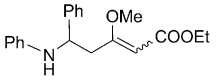
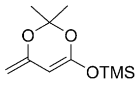
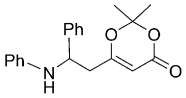
To check the influence of diene conformation, various Brassard dienes[26] and the locked methylenedioxine diene[27] were prepared and engaged in the Sc^{III}-USY catalyzed reaction with *N*-phenyl phenylimine **3a** or its precursors **1a** and **2a** (Table 3, entries 5–10).

Under the conditions used for the Danishefsky diene, Brassard dienes **4b–c** readily reacted, but two adducts were produced and none of them proved to be cyclic as expected from an imino-Diels–Alder type reaction (Table 3, entries 3,4). Spectroscopic evidences revealed the formation of α- and γ-adducts. Starting from 1-ethoxy-1-silyloxybutadiene **4b**, the γ product was the major adduct and the yields were good with, as before, a slight increase with the pre-formed imine (Table 3, entries 5,6). With the more electron-rich 1-ethoxy-1-silyloxy-3-methoxybutadiene **4c**, the reaction only occurred when the imine was pre-formed. Only the γ adduct was observed but it was produced as a *E/Z* mixture (Table 3, entries 7,8). These results were reminiscent of the Mukaiyama-aldol reaction. As suspected from the results with Brassard dienes, the diene **4d**, locked in *S-trans* conformation, gave a single adduct, resulting from an imino-Mukaiyama-aldol reaction. The later was obtained in high yield from the pre-formed imine but in low yield from its starting precursors (Table 3, entries 9,10).

Table 3. Scope of the diene component.



1a 2a 3a

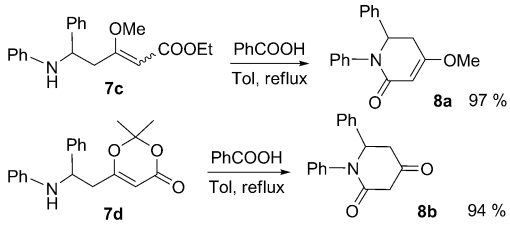
Entry[a]	Diene	t [h]	Yield [%][b]	Adduct
				
1	R = H	48	0	–
2[c]	$R = CH_3$	48	0	–
				
3	**4a**	18	48	**5a**
4[c]	**4a**	2	99	**5a**
				
5	**4b**	18	64	**6b**
				
6[c]	**4b**	2	70	**7b**
				
7	**4c**	24	0	**7c**
8[c]	**4c**	18	59	**7c**
				
9	**4d**	24	15	**7d**
10[c]	**4d**	18	89	**7d**

[a] Reaction performed at room temperature on a 0.5 mmol scale in the presence of 5% of cat. [b] Yields of isolated and purified product; the imine accounted for the mass balance. [c] Starting from the pre-formed imine **3a**.

These results thus confirmed that an aldol pathway[28] always competes with a concerted pathway,[29] even within zeolites. A common siloxonium pathway cannot nevertheless be ruled out.[30] The results also confirmed the role of diene conformation on the course of the reaction, despite the constraints imposed by zeolite cavities.

It is worth noting that these Mukaiyama-type adducts could nevertheless be converted to the corresponding piperidinones in excellent yields (Scheme 5).[31]

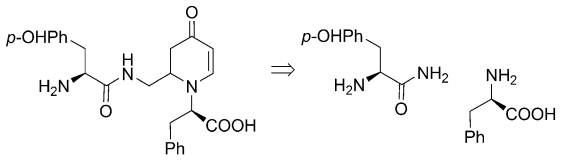
Synthetic application: To highlight the usefulness of this



Scheme 5. Cyclization of the Mukaiyama-type adducts to piperidine derivatives.

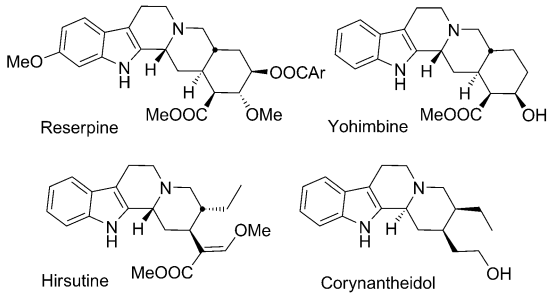
zeo-click catalysis, we applied the present Sc^{III}-USY promoted formation of piperidinones to the synthesis of peptidomimetics and of indolic piperidine alkaloids.

Peptide analogues and modified peptides are of increasing interest as mimics of biologically active peptides and thus as potent drugs.[32] For example, opioid derivatives based on piperidinone as a scaffold have been described and prepared through solid-phase synthesis (Scheme 6).[18c] We thus wondered if the Sc^{III}-zeolite could replace resins, thereby avoiding side reactions during cleavage and low loading.



Scheme 6. Opioid peptide mimics based on piperidinone.

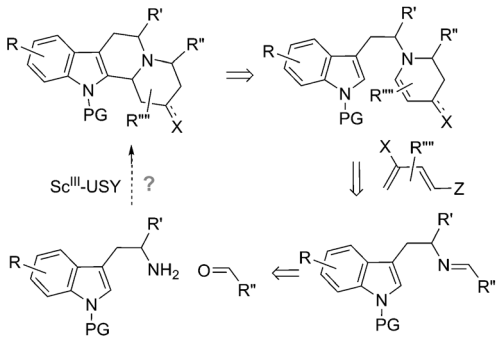
On the other hand, indoloquinolizidine alkaloids such as reserpine, yohimbine hirsutine, and corynantheidol (Scheme 7) exhibit various and interesting properties,



Scheme 7. Some indoloquinolizidine alkaloids.

mostly due to their interaction with adrenoceptors in the nervous system.[33] Some derivatives have also been developed as apoptosis inducers[34] or as inhibitors for protein tyrosine phosphatase B.[35] Such compounds could be obtained in a three-step sequence, with a Diels–Alder type reaction on imine derived from tryptophane or tryptamine, followed by intramolecular cyclization (Scheme 8). The latter is usually performed in acidic media, and the whole sequence can be performed on resin.[35] Due to the dual nature of our heterogeneous catalyst (containing Sc^{III} ions but with protons still present), we expected that further cyclization could also occur, directly leading to indoloquinolizidinones in a one-pot operation and therefore Sc^{III}-zeolites could replace resins and their limitations.

We thus applied the Sc^{III}-zeolite conditions detailed above first to phenylalanine derivatives and then to tryptophane (protected or unprotected). Regardless of the selected starting amino acid, the reaction proceeded well but stopped at the first stage, and gave with the Danishefsky diene the expected piperidinone adducts in good to high yields



Scheme 8. Indoloquinolizidine synthesis.

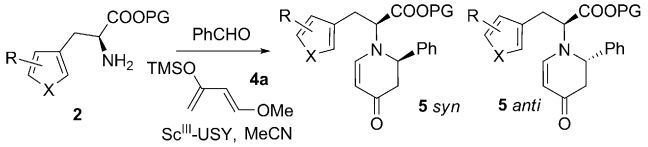
(Table 4). Heating was nevertheless necessary to achieve high yields within reasonable reaction times and again, preforming the imine clearly improved the efficiency of the reaction (Table 4, entries 2 vs. 1, 4 vs. 3, 6 vs. 5, 8 vs. 7, 10 vs. 9, and 12 vs. 11).

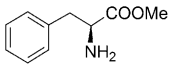
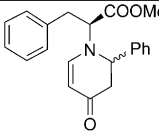
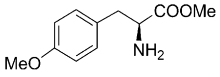
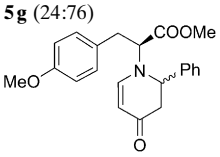
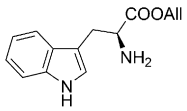
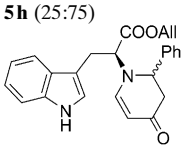
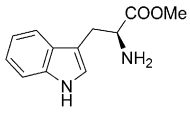
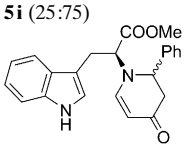
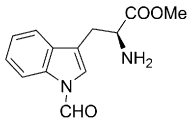
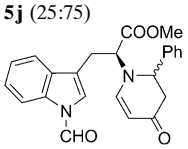
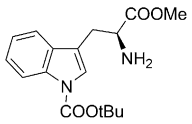
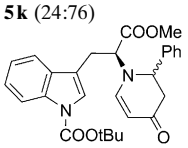
Phenylalanine gave the corresponding adduct in good yields when the imine was pre-formed, whereas no reaction was observed from the starting components (Table 4, entry 2 vs. 1). Tyrosine, as its methyl ether, behaved similarly (Table 4, entry 4 vs. 3) but proved slightly less reactive and the yields were slightly lower (entry 4 vs. 2). Interestingly, tryptophane esters readily reacted with the Danishefsky diene without a protecting group at the *N*-indole moiety. However, the corresponding adduct was obtained with modest yields with an allyl as the carboxylic acid protecting group but in quantitative yields with a methyl group (Table 4, entries 7 and 8 vs. 5 and 6). The allyl group induced the formation of unidentified side-products, whereas the methyl group led to a very clean reaction. Surprisingly, protection at the *N*-indole with carbamates induced a decrease in reactivity, leading to modest but reasonable yields (Table 4, entries 9–12 vs. 7 and 8).

In contrast to solution or resin phase reactions,[12–18] the adducts were always obtained here as the same mixture of diastereoisomers, even when starting from a single imine. Whatever the starting amino acid, the ratios were indeed very similar, with a 3 to 1 mixture, whereas the solution or resin phase synthesis gave ratios from 1 to 1 to 91 to 9. NMR studies of the adducts (and especially of the cyclized products (see below) as well as comparison with the few related known compounds),[34] allowed the assignment of the diastereoisomer stereochemistry as shown in Table 4.

These facts led to interesting mechanistic considerations. Whatever the exact reaction mechanism,[28–30] the fact that the stereodivergent methoxy group in the primary adduct is finally eliminated does not allow for distinguishing between endo or exo pathways, if any. The stereodifference is thus limited to the induction brought by the amino acid stereocenter. Interestingly, an outside Houk-type model[36] can rationalize the stereochemical outcome; interaction of the ester group either with the zeolite or scandium (or both) probably favors the outside arrangement, whereas the spherical shape of the zeolite used (USY) favors a more or less

Table 4. Sc^{III}-catalyzed imino-Diels–Alder reaction of amino acid derivatives (X=NH, NPG or -CH=CH-).



Entry[a]	Amino acid	T [°C]	t [h]	Yield [%][b]	Adduct (d.r.)
					
1	**2e**	60	15	0	–
2[c]	**2e**	60	15	60	**5g** (24:76)
					
3	**2f**	60	15	0	–
4[c]	**2f**	60	15	50	**5h** (25:75)
					
5	**2g**	60	15	traces	–
6[c]	**2g**	60	24	40	**5i** (25:75)
					
7	**2h**	60	15	51	**5j**
8[c]	**2h**	60	15	98	**5j** (25:75)
					
9	**2i**	60	15	traces	–
10[c]	**2i**	60	15	44	**5k** (24:76)
					
11	**2j**	60	15	traces	–
12[c]	**2j**	60	15	50	**5l** (24:76)

[a] Reaction performed at room temperature on a 0.5 mmol scale in the presence of 5% of cat.. [b] Yields of isolated and purified product; the imine accounted for the mass balance. [c] Starting from the pre-formed imine **3a**.

spherical rather than extended transition-state, leading to the *anti* diastereoisomer (Scheme 9).

The presence of protons left in our heterogeneous Sc^{III}-zeolite catalyst suggested that direct cyclization of the Diels–Alder adduct could also occur. However, even upon heating and long exposure, no further reaction was observed, regardless of the solvent used (Table 5, entries 1–3). This might be due to the low amount of protons since only 5 mol% of Sc^{III}-USY was used, leading to an approximate 40 mol% of protons theoretically present in the zeolite. Treatment with the fully acidic H-USY, even in excess, did not help (Table 5, entries 4–6). Only conventional methods were able to produce useful amounts of the desired tetracyclic indoloquinolizidinones (Table 5, entries 7,8), and trifluoroacetic acid in large excess (50–100 equiv) proved to be really efficient, leading to a high yield of the expected indoloquinolizidinones. A small amount of dichloromethane was added for solubility reasons (Table 5, entry 8). It is interesting to note that each dehydropiperidinone diastereoisomer **5*syn*** or **5*anti*** led after cyclization under these conditions to a single indoloquinolizidinone diastereoisomer **9*cis*** or **9*trans*** (Scheme 10; Table 5). Thus, regardless of the stereochemistry of the phenyl group adjacent to the nitrogen atom, the same stereochemistry is produced during the acidic cyclization.

Conclusion

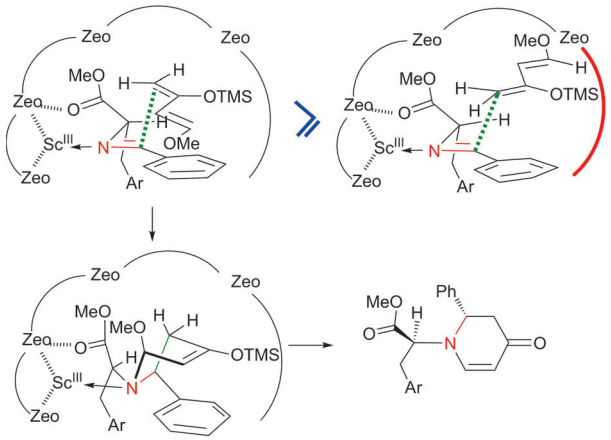
We have developed a new heterogeneous version of the imino-Diels–Alder and Mukaiyama reactions based on Sc^{III}-zeolite as catalyst. The catalyst proved highly efficient, requiring only low loading ($\leq$5 mol% of Sc), and was readily reusable without any loss in reaction efficiency.

Furthermore, this Sc^{III}-USY catalyzed imino-Diels–Alder has been applied to the synthesis of some peptidomimetics and highly complex indoloquinolizidinones. The latter alkaloid related compounds were conveniently obtained in only two steps starting from simple components (amino acids, aldehydes, and electron-rich dienes) with overall yields over 83%.

Experimental Section

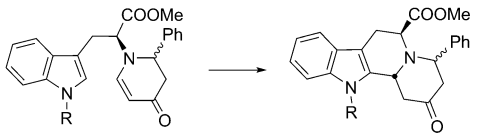
Preparation of Sc^{III}-USY: Commercial NH_4USY was loaded in an oven and heated at 550°C during 4 h to give H-USY. H-USY (1 g) and $Sc(OTf)_3$ (214 mg, 0.1 equiv) were mixed using a mortar and charged in a closed reactor. The mixture of powders was heated at 350°C over three days under a nitrogen flow, quantitatively yielding Sc^{III}-USY.

General procedure for the Sc^{III}-zeolite catalyzed synthesis of pyranones: A suspension of Sc^{III}-USY (34 mg, 0.05 equiv) in acetonitrile (1.5 mL) was added the aldehyde (0.3 mmol, 1 equiv), amine (0.3 mmol, 1 equiv) and the Danishefsky diene (0.45 mmol, 1.5 equiv). Depending on the substrates, the mixture was either maintained at room temperature or heated at 60°C. The reaction was monitored by TLC. After completion of the reaction, the mixture was taken up in dichloromethane (10 mL) then filtered on nylon membranes (0.20 μm). Solvent evaporation provided the resulting crude product, usually at > 95% purity as judged by NMR spectroscopy. When necessary, purifications were performed by silica column chromatography using a mixture of ethyl acetate/cyclohexane as the eluent to afford pure products.



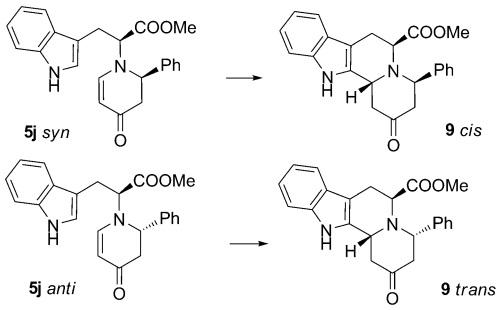
Scheme 9. Possible model accounting for the diastereoselectivity observed in the Sc-USY-catalyzed reaction of imines derived from amino acids.

Table 5. Cyclization of indolic dehydropiperidinones to indoloquinolizidinones.



Entry[a]	Indolic dehydropiperidinone	Reagent	Solvent	T [°C]	Yield [%][b]
1	R = H, CHO, Boc	Sc-USY	CH_2Cl_2	RT to reflux	0
2	R = H, CHO, Boc		MeCN	RT to reflux	0
3	R = H, CHO, Boc		Tol	RT to reflux	0
4	R = H	H-USY	CH_2Cl_2	RT to reflux	0
5	R = H		MeCN	RT to reflux	0
6	R = H		Tol	RT to reflux	0
7	R = H	H_2SO_4	MeOH	reflux	50
8	R = H	CF_3COOH	CH_2Cl_2	0	85

[a] Reaction performed at room temperature on 0.5 mmol. [b] Yields of isolated and purified product; the imine accounted for the mass balance.



Scheme 10. Cyclization of indolyl dehydropiperidinones to indoloquinolizidinones.

Data for selected products: *(S) Ethyl 2-(4-oxo-2-phenyl-3,4-dihydropyridin-1(2H)-yl)-3-phenylpropanoate*: 5 g colorless oil (60 % yield); diastereoisomeric ratio (d.r.) 24:76 *syn/anti*. *Anti isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.0 Hz, 1H, 7.31–7.28 (m, 4H), 7.18 (t, J = 7.5 Hz, 2H), 6.99 (dd, J = 6.0, 3.1 Hz, 2H), 6.81 (dd, J = 7.5, 1.5 Hz, 2H), 5.24 (d, J = 7.7 Hz, 1H), 4.62 (dd, J = 13.1, J = 5.4, 1H), 4.11 (q, J = 7.3, 2H), 3.74 (dd, J = 10.0, 5.8 Hz, 1H), 3.16 (dd, J = 14.0, 5.7 Hz, 1H), 2.95 (dd, J = 14.0, 10.0 Hz, 1H), 2.62 (dd, J = 16.3, 13.7 Hz, 1H), 2.49 (ddd, J = 16.5, 5.0, 0.7 Hz, 1H), 1.21 ppm (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7 (C), 170.7 (C), 151.0 (CH), 137.9 (C), 136.2 (C), 129.7 (2CH), 129.2 (2CH), 128.8 (CH), 128.7 (2CH), 127.84 (2CH), 127.31 (CH), 101.7 (CH), 64.5 (CH), 62.7 (CH2), 61.9 (CH), 44.8 (CH_2), 36.7 (CH_2), 14.4 ppm (CH_3); HRMS (ESI+): m/z calcd for $C_{22}H_{24}NO_3$ 350.175 $[M+H]^+$; found: 350.171 . *Syn* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, J = 7.9 Hz, 1H), 7.30–7.23 (m, 5H), 7.11–7.06 (m, 4H), 5.16 (d, J = 7.9 Hz, 1H), 4.06 (q, J = 7.1 Hz, 2H), 4.01 (dd, J = 7.7, 7.5 Hz, 1H), 3.89 (dd, J = 10.0, 5.4 Hz, 1H), 3.16 (dd, J = 13.6, 5.1 Hz, 1H), 2.96 (dd, J = 13.7, 10.0 Hz, 1H), 2.52 (d, J = 7.7 Hz, 2H), 1.13 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7 (C), 170.5 (C), 150.9 (CH), 138.9 (C), 136.3 (C), 129.4 (2CH), 129.1 (2CH), 129.0 (2CH), 128.6 (CH), 127.5 (CH), 127.3 (2CH), 100.2 (CH), 64.7 (2CH), 61.8 (CH_2), 44.1 (CH_2), 38.8 (CH2), 14.1 ppm (CH_3). HRMS (ESI+): m/z calcd for $C_{22}H_{24}NO_3$: 350.175 $[M+H]^+$, found: 350.171.

(4R,6S,12bR) Methyl 2-oxo-4-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3a]quinolizine-6-carboxylate ***9 cis***: Colorless oil, 85 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (bs, 1H), 7.47–7.42 (m, 3H), (7.36 (t, J = 7.4 Hz, 2H), 7.31 (d, J = 7.4 Hz, 2H), 7.15 (dd, J = 7.8 Hz, 1H), 7.10 (dd, J = 7.9, 6.8 Hz, 1H), 5.08 (dd, J = 5.8, 4.5 Hz, 1H), 4.15 (dd, J = 9.3, 4.2 Hz, 1H), 3.96 (dd, J = 6.6, 2.0 Hz, 1H), 3.57 (s, 3H), 3.18 (dd, J = 14.5, 6.2 Hz, 1H), 3.12 (ddd, J = 16.5, 2.1, 1.7 Hz, 1H), 3.03 (ddd, J = 16.4, 6.8, 2.2 Hz, 1H), 2.84–2.78 (m, 2H), 2.48 ppm (ddd, J = 14.1, 4.3, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.45 (C), 173.13 (C), 141.2 (C), 136.2 (C), 131.7 (C), 129.1 (2CH), 128.3 (CH), 127.6 (2CH), 127.2 (C), 122.2 (CH), 119.9 (CH), 118.4 (CH), 111.4 (CH), 106.2 (C), 62.25 (CH), 57.92 (CH), 52.3 (CH_3), 51.6 (CH), 48.8 (CH_2), 43.8 (CH_2), 20.45 ppm (CH_2); HRMS (ESI+): m/z calcd for $C_{23}H_{22}N_2O_3Na$: 397.1528 $[M+Na]^+$; found: 397.152.

Acknowledgements

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