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Scandium(III) Zeolites as New Heterogeneous Catalysts: [4+2]Cyclocondensation of in situ Generated Aryl Imines with Alkenes

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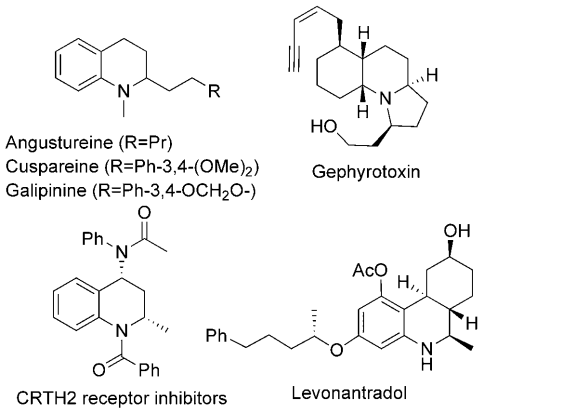
Abstract: Scandium(III)-exchanged zeolite was used as heterogeneous ligand-free catalysts for the [4+2]cyclocondensation of amines and aldehydes with alkenes through the in situ formation of imines. Such catalysts offered a versatile, efficient, and highly regio- and stereoselective synthesis of tetrahydroquinoline derivatives. These catalysts exhibited a wide scope and compatibility with functional groups. They are very simple to use, easy to remove (by simple filtration), and they are recyclable (up to three times without loss of activity).

Keywords: catalysis · cycloaddition · imines · scandium · zeolites

Introduction

Quinoline and its hydrogenated forms represent a very important subclass of alkaloid natural products.[1] Such motifs can be found in organisms as different as plants with *i.a.* angustura, a Venezuelan tree used in folk medicine principally to combat fevers (Scheme 1, top left)[2] and frogs with the neurotoxins excreted on their skins (Scheme 1, top right).[3] Among them, tetrahydroquinolines exhibit the largest range of activities.[4] They are not only used or developed as antibacterial agents,[5] as antitumor agents,[6] as HIV protease inhibitors,[7] as therapeutic agents for *i.a.* allergic diseases triggered by prostaglandin (CRTH2 inhibitors; Scheme 1),[8] or for antiemetic and analgesic effects through activation of cannabinoid receptors (Levonantradol, Scheme 1),[9] but also as compounds for altering the lifespan of eukaryotic organisms[10] or imaging G protein-coupled estrogen receptors.[11]



Scheme 1. Examples of biologically active natural tetrahydroquinolines and related drugs and therapeutic agents.

Therefore, a considerable number of synthetic approaches towards (hydro)quinoline derivatives have been developed.[12] Among them, the formal [4+2]cycloaddition reactions between *N*-arylimines acting as heterodienes towards dienophiles have long been recognized as one of the most convenient and rapid methods for the synthesis of (hydro)-quinolines. Usually performed under acidic conditions, such cycloadditions have been reported with various Lewis acid catalysts, such as bismuth(III) bromide,[13] niobium(V) chloride,[14] samarium diiodide,[15] cerium(IV) ammonium nitrate,[16] magnesium perchlorate,[17] copper(II) bromide,[18] indium trichloride,[19] and lanthanide salts.[20] However, supported and reusable catalysts remained scarcely used despite obvious advantages, and only indium trichloride supported on polyaniline,[21] antimony chloride on hydroxyapatite,[22]

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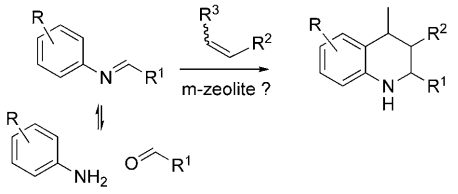
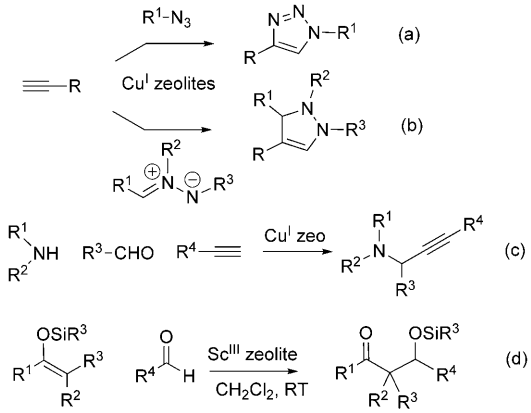
lanthanide polyoxometalate,[23] and montmorillonites[24] have so far been mentioned. This relative lack led us to consider applying metal-doped zeolites as catalysts for such cycloadditions (Scheme 2), in connection with our recent zeo-click syntheses.[25–28]



Scheme 2. Possible metal-doped zeolite-catalyzed cycloaddition of imines with alkenes.

We indeed recently demonstrated that Cu^{I} zeolites are very effective and reusable catalysts for the cycloaddition of alkynes with azides or azomethine imines (Scheme 3a and b).[25,26] Therefore, other cycloadditions, such as the reaction of *N*-arylimines with alkenes should be amenable under similar conditions. Moreover, we also showed that one-pot multicomponent reactions could also be catalyzed by Cu^{I} zeolites (Scheme 3c).[27] Since the latter proceeds by the in situ formation of imines, it was thus tempting to examine a direct one-pot reaction from aldehydes and amines in the presence of alkenes. On the other hand, we also recently showed that Sc^{III} zeolites are useful and reusable catalysts for Mukaiyama-type aldolizations (Scheme 3d).[28] Lanthanide and Sc^{III} salts are known to promote hetero-Diels–Alder reactions.[29] Thus, Sc^{III} zeolites seem good candidates for catalyzing cycloadditions leading to hydroquinolines.



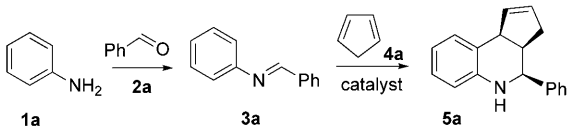
Scheme 3. Selected reactions catalyzed by m-zeolites.

We report here our results in this area, revealing the first zeolite-catalyzed cycloaddition of *N*-arylimines with alkenes for the synthesis of hydroquinolines (Scheme 2).

Results and Discussion

Set up of reaction conditions: In a first series of experiments, we examined the behavior of the stable (*E*)-imine **3a**, readily accessible from aniline (**1a**) and benzaldehyde (**2a**), with cyclopentadiene (**4a**) in the presence of USY zeolites modified with different metals under various conditions (Table 1). This zeolite was selected first, since upon metal doping, it proved efficient for other organic transformations[24–26] and because it holds large pores, able to accommodate several molecules together.

Table 1. Condition screening for the m-doped zeolite-catalyzed cycloaddition of *N*-phenylbenzimine or its precursors with cyclopentadiene.[a]



Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Recovered **3a** [%][b]	Yield of **5a** [%][b]
1	none	CH_2Cl_2[c]	20	72	98	0
2	CuI	CH_2Cl_2[c]	20	72	80–97	traces
3	$CuBr_2$	CH_2Cl_2[c]	20	24	99–58	0–41
4	Cu^{I}-USY	CH_2Cl_2[c]	20	72	99	0
5	Cu^{II}-USY	CH_2Cl_2[c]	20	72	97	traces
6	Sc^{III}-USY	PhMe	60	72	79	16
7	Sc^{III}-USY	CH_2Cl_2	40	12	80	12
8	Sc^{III}-USY	THF	60	24	81	4
9	Sc^{III}-USY	MeCN	60	18	2	96
10	Sc^{III}-USY	MeOH	20	24	58	23
11	H-USY	MeCN	20	48	95	traces

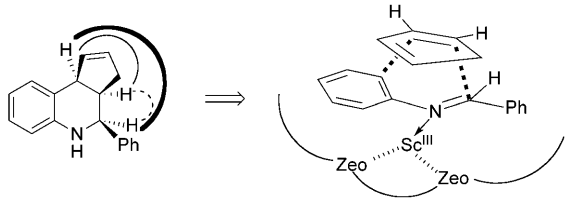
[a] Reaction performed on 0.3 mmol of **1a**, 0.3 mmol of **2a**, and 0.45 mmol of **4a** in 1 mL of solvent, with 7–10 mg of Sc^{III} zeolite (i.e., approximately 5 mol% of Sc^{III}[30]). [b] Yields of isolated pure product, obtained as a single diastereoisomer. [c] Toluene, THF, acetonitrile, and methanol were also examined without success.

No reaction took place without catalyst whatever the solvent (Table 1, entry 1). Cu^{I} alone was not a true catalyst, only giving a very small amount of the expected adduct **5a** in very low yield (entry 2). As reported,[18] Cu^{II} salts alone did catalyze the cycloaddition and led to the expected adduct **5a** although in moderate yield in a slow reaction (entry 3). Under similar conditions, Cu^{I}- as well as Cu^{II}-USY were not effective as catalysts and only traces of adduct could be detected after a prolonged reaction time while the starting materials were mostly recovered (entries 4–5). Rewardingly, Sc^{III}-USY gave the expected adduct **5a** in low to high yields depending on the solvent used (entries 6–10). A slow but clean transformation was observed in apolar or slightly polar solvents and despite heating, the adduct **5a** was isolated with modest yields (entries 6–7). Surprisingly, in more polar solvents, such as THF, the reaction was even lower although the conversion was similar (entry 8 vs. 6–7). In sharp contrast, acetonitrile allowed the adduct **5a** to be obtained in excellent and almost quantitative yield (entry 9).

Protic solvents, such as methanol, slowed the reaction again and only modest yields could be achieved (entry 10).

Control experiments with the native H-USY showed its total inactivity, confirming the key role of scandium ions loaded into the zeolite during this reaction (entry 11). As expected, the same results were obtained when starting from aniline (**1a**) and benzaldehyde (**2a**), in situ leading to imine **3a**.

Interestingly, a single regio- and diastereoisomer was isolated in these experiments with cyclopentadiene. Comparison of NMR spectroscopic data with known data[19,31] and further NOESY experiments revealed the all-*cis* stereochemistry of the **5a** adduct. This result suggested a [4+2]cycloaddition with a concerted *endo* mechanism (Scheme 4; see the mechanism section below).



Scheme 4. Observed NOESY proximities and the resulting hypothetic *endo* [4+2]pathway for the reaction catalyzed by Sc zeolite.

Catalyst recycling: An important and useful feature of any heterogeneous catalyst is its recovery and recyclability. The Sc-doped zeolites could easily be recovered through a simple filtration over Nylon membrane. A simple wash allowed us to recover the organic materials on one hand and on the other, the Sc^{III} zeolite.

The recyclability was examined by performing the one-pot imine formation–cycloaddition reaction between aniline (**1a**), benzaldehyde (**2a**), and cyclopentadiene (**4a**) with the same Sc^{III}-USY catalyst several times. At each run, the catalyst was recovered by filtration and regenerated or not by heating before being reused in the next run. As shown in Figure 1, the catalyst could be recycled at least up to five times, but the catalyst efficiency dramatically changed upon regeneration or not between each run (Figure 1, back and front row, respectively). A slight decrease in yields occurred every two runs with regeneration through heating at 550 °C (Figure 1, back row), whereas a sharp drop was observed after the first run without regeneration (Figure 1, front row). Nevertheless, the catalyst was still active after the 5th reuse, still giving the product with a reasonable 47 % isolated yield with regeneration.

Scope and limitations: With these conditions in hand, we then explored the scope of this heterogeneously catalyzed cyclocondensation. In one series of experiments, various anilines **1a–e** were submitted to benzaldehyde (**2a**) in the presence of cyclopentadiene (**4a**) and a catalytic amount of Sc^{III}-USY (5 mol %) as the catalyst in acetonitrile (Table 2). At room temperature, the simplest aniline gave the expected

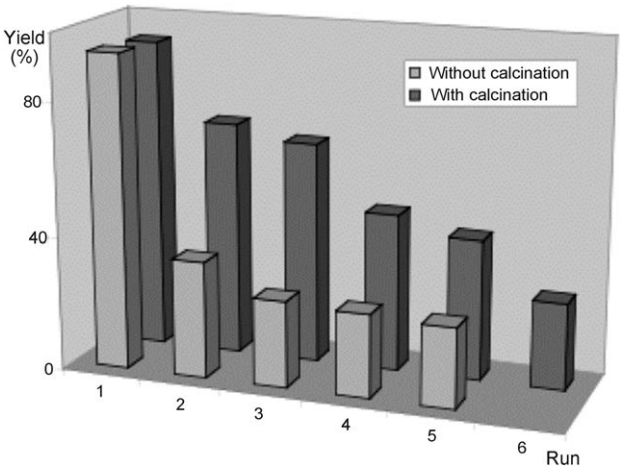
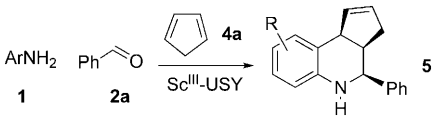
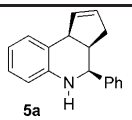
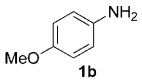
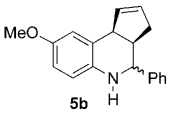
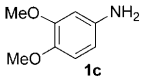
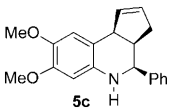
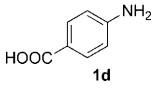
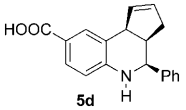
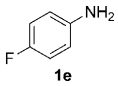
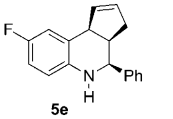


Figure 1. Sc^{III}-USY recycling and reuse for the one-pot imine formation—cycloaddition reaction between benzaldehyde (**1a**), aniline (**2a**), and cyclopentadiene (**4a**).

Table 2. Sc^{III}-USY-catalyzed cycloaddition of various anilines **1** with benzaldehyde.[a]



Entry	Amine	*T* [°C]	Yield [%][b]	Ratio *cis*/*trans*[c]	Adduct
1	 **1a**	20	40	100:0	 **5a**
2		60	96	100:0	
3	 **1b**	60	35	79:21	 **5b**
4	 **1c**	60	29	100:0	 **5c**
5	 **1d**	60	47	100:0	 **5d**
6	 **1e**	60	51	100:0	 **5e**

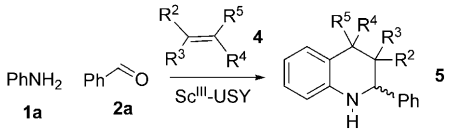
[a] Reactions performed with 1 equiv of **1**, 1 equiv of **2a**, 1.5 equiv of **4a**, and 5 mol % Sc^{III}-USY[30] in 2 mL of acetonitrile over 18 h. [b] Yields of isolated pure product. The starting amine and aldehyde usually accounted for the mass balance. [c] Determined by NMR spectroscopic analysis of the crude mixtures.

adduct but with a modest yield, whereas at 60 °C the reaction was quantitative (Table 2, entry 1 vs. 2). Under both conditions, the reaction was completely regio- and stereoselective, yielding a single regio- and diastereoisomer. With methoxy groups on the aniline, the reaction became less ef-

fective, even upon heating (entries 3–4). Surprisingly, the presence of one *para*-methoxy group induced a drop in stereoselectivity, whereas with one *para*- and one *meta*-methoxy group, the very high *cis* stereoselectivity was maintained (entry 3 vs. 4). Electron-withdrawing groups instead of -donating groups did not reverse the yield lowering and whatever the electron-withdrawing character of the group, moderate yields were achieved (entries 5–6). Nevertheless, a single *cis* adduct was again produced in each case.

In a second series of experiments, various alkenes **4a**–**d** were examined, and thus submitted to aniline (**1a**) and benzaldehyde (**2a**) under the same conditions (Table 3). Enol

Table 3. Sc^{III}-USY-catalyzed cyclocondensation of various alkenes **4** with aniline and benzaldehyde.[a]



Entry	Alkene	*T* [°C]	Yield [%][b]	Ratio *cis*/*trans*[c]	Adduct
1		20	40	100:0	
2	**4a**	60	96	100:0	**5a**
3		20	76	63:37	
4	**4b**	0	70	62:38	**5f**
5		20	34	48:52	
6	**4c**	60	23	69:31	**5g**
7	OEt **4d**	60	60	0:100	OEt **5h**

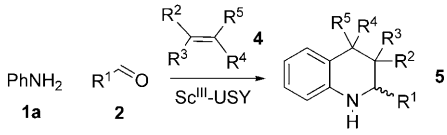
[a] Reactions performed with 1 equiv of **1**, 1 equiv of **2a**, 1 equiv of **4a**, and 5 mol% Sc^{III}-USY,[30] in 2 mL of acetonitrile over 18 h. [b] Yields of isolated pure product. The starting amine and aldehyde usually accounted for the mass balance. [c] Determined by NMR spectroscopic analysis of the crude mixture.

ethers were clearly more reactive than cyclopentadiene at room temperature, as revealed by reactions with dihydrofuran and ethyl vinyl ether (Table 3, entries 3–4, 7 vs. 1–2). With the former, the reaction could even be performed at 0°C without dramatic changes in yield and stereoselectivity (entry 4 vs. 3 vs. 1). In contrast, dihydropyrane did not react as well, even at 60°C. At room temperature, the corresponding adduct was formed with low yield and almost no stereoselectivity, but at 60°C the stereoselectivity was improved but to the detriment of yield (entry 6 vs. 5 vs. 1).

With such enol ethers, the regioselectivity was still very high and a single regioisomer was observed (Table 3, entries 3–4, 5–6, 7). However, the stereoselectivity was dramatically lowered (entries 3–4, 5–6 vs. 1–2), except with ethyl vinyl ether, which again provided a single adduct (entry 7). However, its stereoselectivity was established as *trans* by comparison with known compounds[32] and by NOESY experiments. This stereochemical reversion suggests another but not concerted mechanism with enol ethers (see the mechanism section below).

In a third series of experiments, various aldehydes **2a**–**h** were examined (Table 4). As for anilines (Table 2), benzaldehydes carrying electron-donating or -withdrawing groups

Table 4. Sc^{III}-USY-catalyzed cyclocondensation of various aldehydes **2** and aniline with cyclopentadiene or dihydrofurane.[a]



Entry	Aldehyde	Alkene	Yield [%][b]	Ratio[c] *cis*/*trans*	Adduct
1	PhCHO		40	100:0	
2	**2a**	**4a**	96	100:0	**5a**
3	*p*MePhCHO **2b**	**4a**	32	100:0	Ph*p*Me **5i**
4	*p*MeOPhCHO **2c**	**4a**	13	100:0	Ph*p*OMe **5j**
5	*p*FPhCHO **2d**	**4a**	63	100:0	Ph*p*F **5k**
6	*p*O_2NPhCHO **2e**	**4a**	50	100:0	Ph*p*NO_2 **5l**
7	CHO **2f**	**4a**	40	100:0	**5m**
8	CHO **2f**	**4b**	10	n.d.	**5n**
9	CHO **2g**	**4a**	58	100:0	**5o**
10	CHO **2g**	**4b**	62	88:12	**5p**

Table 4. (Continued)

Entry	Aldehyde	Alkene	Yield [%][b]	Ratio[c] *cis*/*trans*	Adduct
11	EtOOC−CHO **2h**	**4a**	96	100:0	**5q**
12	EtOOC−CHO **2h**	**4b**	95	72:28	**5r**

[a] Reactions performed with 1 equiv of **1**, 1 equiv of **2a**, 1 equiv of **4a**, and 5 mol% Sc^{III} -USY,[30] in 2 mL of acetonitrile over 18 h. [b] Yields of isolated pure product. The starting amine and aldehyde usually accounted for the mass balance. [c] Determined by NMR spectroscopic analysis of the crude mixture.

proved to be less reactive and they required heating (Table 4, entries 3–6 vs. 1–2). The presence of an electron-donating group was particularly deleterious, inducing low yields of adducts, and the more electron-donating the group, the lower the yield (entry 4 vs. 3). Although the effect of the withdrawing groups was less dramatic with modest to good yields of adducts, the same tendency was observed (entry 5 vs. 6). In contrast, all these reaction gave a single adduct of *cis* stereochemistry.

Heteroaromatic aldehydes were also less reactive, leading to modest yields of the corresponding adducts (Table 4, entries 7–8), even with more reactive dienes, such as dihydrofuran (entry 8 vs. 7).

Aliphatic aldehydes gave better results and the expected adducts between isobutyraldehyde (**2g**) and cyclopentadiene or dihydrofuran were isolated in good yields (Table 4, entry 9–10). As for the preceding examples, a single adduct was formed with cyclopentadiene, whereas a mixture of stereoisomers was obtained with dihydrofuran.

Ethyl glyoxylate (**2h**) proved to be very reactive, giving the expected adducts **5q–r** with cyclopentadiene or dihydrofurane in almost quantitative yields at room temperature (Table 4, entries 11 and 12). Again, a single adduct was formed with cyclopentadiene, and a mixture of diastereoisomers but with the same very high regioselectivity was obtained with dihydrofuran (see NOESY in the Supporting Information).

Mechanism: The mechanism of aza-Diels–Alder reactions is still a matter of debate. Under classical conditions, that is, in the presence of a Lewis acid, a concerted Diels–Alder type mechanism is often proposed,[33] although a delicate balance between normal and reverse electron demand is invoked to explain differences in reactivity and stereoselectivity.[19d,31,34] However, evidence for a stepwise cationic mechanism has been reported.[35]

Organic reactions performed in zeolites could occur with mechanisms similar or different from the same reaction in homogeneous conditions, as observed for Cu^{I}-zeolite-catalyzed reactions.[25–28] The present Sc^{III}-zeolite-catalyzed cyclocondensations could thus follow either normal or reverse electron demand Diels–Alder pathways or a stepwise cationic route, or both of them.

The differences in stereoselectivity observed here with cyclopentadiene (see Table 1) relative to other alkenes (see Table 2) suggested that different mechanisms operated in these cyclocondensations. To look for such mechanistic duality, correlations between Hammet coefficients and various reaction parameters are often used.[36] We thus evaluated the Sc^{III}-zeolite-catalyzed reaction efficiency upon substituent effects (Figure 2). Both *para*-substituted anilines and benzaldehydes showed similar trends with maximum yields for nonsubstituted substrates and decreasing yields for substrates with either electron-donating or -withdrawing substituents.

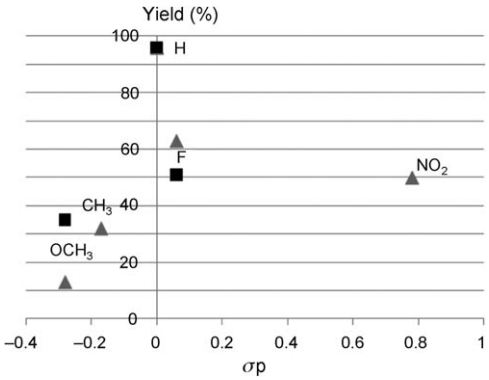
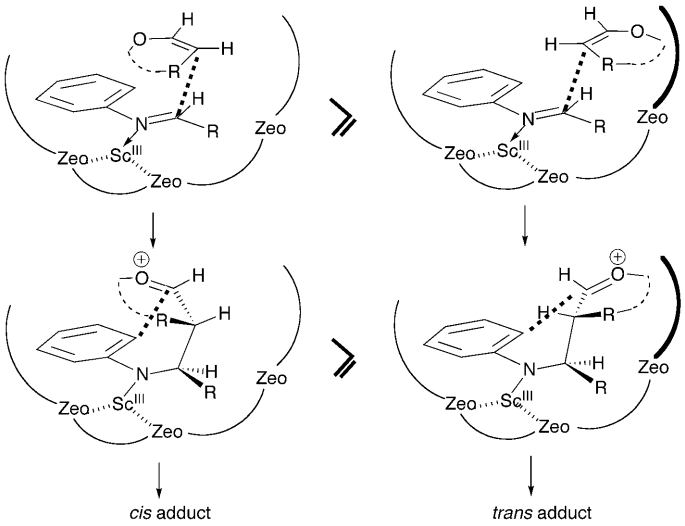


Figure 2. Correlation between yields and the substitution of either aniline or benzaldehyde (◆: aldehyde; ■: aniline).

The presence of two different slopes in the correlation graphic confirms the implication of different mechanisms in this Sc^{III}-zeolite-catalyzed cyclocondensation (Figure 2). For electron-withdrawing groups, the dependence of the reaction efficiency on Hammet parameters and the formation of a single diastereoisomer point to a normal electronic demand concerted reaction (Scheme 4, right). On the other hand, the isolation of two different diastereoisomers from *para*-methoxyaniline suggests a dominant stepwise mechanism for electron-donating-substituted substrates. The latter mechanism is also supported by the reactions of enol ethers, which gave a mixture of diastereoisomers, and by the rise in diastereoselectivity upon a rise in temperature to above room temperature for dihydropyrane and the reversal of selectivity observed with ethyl vinyl ether (Table 3).

It is worth noting that literature precedents for reactions with enol ethers often mentioned mixtures of diastereoisomers, with the *cis* isomer as a major product for Sm^{III}, Ce^{IV}, or Ti^{IV} as the catalyst[15,16,32] but with the *trans* as the major product in the presence of Yb^{III}, I_2, TMSCl, or even 4-nitro-

phtalic or phosphomolybdic acids.[37] The overall *cis* preference observed with Sc^{III} zeolite whatever the "dienophile" could also be due to the spherical shape of the zeolite used (USY), favoring more or less spherical rather than extended transition states, especially in the stepwise mechanism (Scheme 5).



Scheme 5. Proposed stepwise mechanism taking into account the spherical shape of the Sc-USY used as the catalyst (the bold curve indicates steric repulsion between the "dienophilic" part and zeolite wall).

Conclusion

We have shown for the first time that scandium(III)-modified zeolites can be used as catalysts for the aza-Diels–Alder reaction of imines with alkenes. This heterogeneous method offers a mild and efficient access to tetrahydroquinoline derivatives with a reasonably wide scope, tolerating various functional groups, and with high regioselectivity. Moreover, this heterogeneous scandium (III)-modified zeolite catalyst can be reused at least three times without significant loss of activity.

Experimental Section

General: All starting materials were commercial (used as received) or prepared according to known literature procedures (see the Supporting Information for details). The reactions were monitored by TLC carried out on silica plates (silica gel 60 F254, Merck) by using UV-light and phosphomolybdic acid with cerium(IV) for visualization. Column chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck) by using mixtures of ethyl acetate or toluene and cyclohexane as the eluents. Evaporation of the solvents was conducted under reduced pressure at temperatures less than 30 °C. Melting points (M.p.) were measured in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts δ and coupling constants J are given in ppm and Hz, respectively. Chemical shifts δ are reported relative to residual solvent as an internal standard ([D$_1$]chloroform: $\delta = 7.24$ for ^{1}H and 77.23 ppm for ^{13}C). Carbon multiplicities were determined by DEPT135 experiments. The *cis*/*trans* conformation of the products was determined by NOESY experiments. Electrospray (ESIMS) low/high-resolution mass spectra were obtained from the mass spectrometry department of the Service Commun d'Analyses, Institut de Chimie, Strasbourg.

Preparation of Sc^{III} zeolites

Sc^{III}-USY: Commercial NH_4USY was loaded in an oven and heated at 550 °C during 4 h giving H-USY. H-USY (1 g) and $Sc(OTf)_3$ (214 mg, 0.1 equiv) were mixed by using a mortar and charged in a closed reactor. The mixture of powders was heated at 350 °C during over three days under a nitrogen flow, quantitatively yielding Sc^{III}-USY. These modified zeolites have been fully characterized and this will be described in a more specific article.

General procedure for the Sc^{III}-zeolite-catalyzed [4+2]cyclocondensation of anilines, aldehydes, and alkenes: Aniline **1** (0.5 mmol, 1.0 equiv), aldehyde **1** (0.5 mmol, 1.0 equiv), and then alkene **4** (0.75 mmol, 1.5 equiv) were successively added to a suspension of Sc^{III}-USY (45 mg, 0.05 equiv)[30] in acetonitrile (2 mL). After 18 h stirring at 20 or 60 °C (see Tables 1–4), the mixture was cooled to room temperature and the catalyst was removed by filtration over Nylon membrane (0.20 μm). Solvent evaporation provided the resulting crude product. Column chromatography was performed when necessary.

Some of the so-formed adducts are known compounds, and hydroquinolines **5a**[38] **5b**,[39] **5c**,[40] **5d**,[41] **5f**,[42] **5g**[15] **5h**,[32] **5I**,[39] **5l**,[40] and **5n**[37b] have been reported.

8-Fluoro-4-phenyl-3a,4,5,9b-tetrahydro(3*H*)cyclopenta[*c*]quinoline (5e): Only the *cis* adduct was obtained. Yield: 51 %; pale-green solid; m. p. 113 °C; ^{1}H NMR (300 MHz, CDCl3): $\delta = 7.43$–7.36 (m, 2H), 7.08–7.00 (m, 3H), 6.97 (d, $J = 7.6$ Hz, 1H), 6.75 (dd, $J = 7.9$, 7.1 Hz, 1H), 6.61 (d, $J = 7.9$ Hz, 1H), 5.84 (dm, $J = 5.4$, 1.5 Hz, 1H), 5.64 (ddd, $J = 5.5$, 2.3, 1.8 Hz, 1H), 4.61 (d, $J = 3.3$ Hz, 1H), 4.09 (d, $J = 8.9$ Hz, 1H), 3.69 (brs, 1H), 2.95 (qd, $J = 9.0$, 3.4 Hz, 1H), 2.60 (ddddd, $J = 16.3$, 9.4, 2.7, 2.4, 2.1 Hz, 1H), 1.79 ppm (dddd, $J = 16.0$, 8.7, 2.5, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.7$ (d, $J_{C-F} = 236$ Hz), 142.8, 141.9, 133.6, 131.1, 128.7, 127.7 (d, $J_{C-F} = 6$ Hz), 127.5, 126.6, 116.6 (d, $J_{C-F} = 7$ Hz), 115.0 (d, $J_{C-F} = 22$ Hz), 113.0 (d, $J_{C-F} = 23$ Hz), 58.6, 46.9, 45.8, 31.7 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{18}H_{17}FN$: 266.134; found: 266.134 $[M+H]^+$.

4-(4-Methoxyphenyl)-3a,4,5,9b-tetrahydro(3*H*)cyclopenta[*c*]quinoline (5j): Only the *cis* adduct was obtained. Yield: 13 %; pale-yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$ (d, $J = 8.5$ Hz, 2H), 7.04 (d, $J = 7.0$ Hz, 1H), 6.97 (td, $J = 7.7$, 1.4 Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 2H), 6.73 (td, $J = 7.4$, 1.2 Hz, 1H), 6.60 (dd, $J = 7.9$, 1.0 Hz, 1H), 5.85–5.80 (m, 1H), 5.66–5.61 (m, 1H), 4.57 (d, $J = 3.3$ Hz, 1H), 4.08 (d, $J = 9.1$ Hz, 1H), 3.81 (s, 3H), 3.70 (brs, 1H), 2.95 (qd, $J = 9.0$, 3.3 Hz, 1H), 2.62 (dddd, $J = 16.5$, 9.4, 4.4, 2.2 Hz, 1H), 1.82 ppm (dddd, $J = 16.0$, 8.8, 2.5, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.9$, 145.9, 135.1, 134.2, 130.6, 129.2, 127.7, 126.5, 126.3, 119.3, 116.0, 114.0, 57.7, 55.5, 46.6, 46.3, 31.7 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{19}H_{20}NO$: 278.154; found: 278.152 $[M+H]^+$.

4-(4-Fluorophenyl)-3a,4,5,9b-tetrahydro(3*H*)cyclopenta[*c*]quinoline (5k): Only the *cis* adduct was obtained. Yield: 19 %; pale-brown solid; m. p. 146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$–7.36 (m, 2H), 7.09–7.00 (m, 3H), 6.97 (d, $J = 7.6$ Hz, 1H), 6.75 (t, $J = 7.5$ Hz, 1H), 6.61 (d, $J = 6.9$ Hz, 1H), 5.86–5.82 (m, 1H), 5.65–5.63 (m, 1H), 4.61 (d, $J = 3.3$ Hz, 1H), 4.09 (d, $J = 8.4$ Hz, 1H), 3.69 (brs, 1H), 2.95 (qd, $J = 9.0$, 3.4 Hz, 1H), 2.60 (ddq, $J = 16.3$, 9.4, 2.4 Hz, 1H), 1.79 ppm (dddd, $J = 16.1$, 8.3, 2.3, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.2$ (d, $J_{C-F} = 244$ Hz), 145.6, 138.8, 134.2, 130.5, 129.2, 128.2 (d, $J_{C-F} = 8.6$ Hz), 126.6, 126.2, 119.5, 116.2, 115.5 (d, $J_{C-F} = 19$ Hz), 57.7, 46.5, 46.3, 31.6 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{18}H_{17}FN$: 266.134; found: 266.134 $[M+H]^+$.

4-(Furan-2-yl)-3a,4,5,9b-tetrahydro(3*H*)cyclopenta[*c*]quinoline (5m): Only the *cis* adduct was obtained. Yield: 39 %; white solid; m. p. 104 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.38$ (d, $J = 1.7$ Hz, 1H), 7.05 (d, $J = 7.8$ Hz, 1H), 6.98 (td, $J = 7.7$, 1.8 Hz, 1H), 6.76 (td, $J = 7.4$, 1.3 Hz, 1H), 6.63 (dd, $J = 7.9$, 1.1 Hz, 1H), 6.36 (dd, $J = 3.1$, 1.8 Hz, 1H), 6.25 (dt, $J =$

3.2, 0.8 Hz, 1H), 5.82–5.78 (m, 1H), 5.68–5.66 (m, 1H), 4.63 (d, J= 3.3 Hz, 1H), 4.09 (d, J=8.9 Hz, 1H), 3.85 (brs, 1H), 3.19 (qd, J=8.9, 3.3 Hz, 1H), 2.65 (ddq, J=16.5, 8.8, 2.4 Hz, 1H), 2.17 ppm (ddt, J=16.5, 8.9, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=155.9, 145.1, 141.7, 134.2, 130.5, 129.2, 126.5 (2C), 119.7, 116.1, 110.4, 105.5, 56.8, 46.3, 42.7, 32.7 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{16}H_{16}NO$: 238.123; found: 238.124 $[M+H]^+$.

4-Isopropyl-3a,4,5,9b-tetrahydro(3*H*)cyclopenta[*c*]quinoline (5o): Only the *cis* adduct was obtained. Yield: 58%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.98 (d, J=7.6 Hz, 1H), 6.93 (ddd, J=7.8, 7.5, 1.5 Hz, 1H), 6.68 (td, J=7.4, 1.3 Hz, 1H), 6.55 (d, J=7.8 Hz, 1H), 5.81 (dtd, J=5.7, 2.8, 1.5 Hz, 1H), 5.69 (ddd, J=5.8, 2.5, 1.6 Hz, 1H), 3.94 (d, J=3.9 Hz, 1H), 3.63 (brs, 1H), 2.94 (dddd, J=9.9, 3.5, 2.8, 2.4 Hz, 1H), 2.51 (ddq, J=16.0, 9.0, 2.4 Hz, 1H), 2.23 (dddd, J=16.1, 8.4, 2.4, 1.7 Hz, 1H), 1.66 (ddm, J=13.3, 9.4, 6.5 Hz, 1H), 1.05 (d, J=6.5 Hz, 3H), 1.00 ppm (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=145.8, 134.6, 130.4, 129.5, 129.0, 126.3, 118.9, 115.7, 60.4, 46.6, 41.2, 31.1, 30.8, 20.3, 19.5 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{15}H_{20}N$: 214.160; found: 214.159 $[M+H]^+$.

4-Isopropyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (5p): Yield: 62%; *cis*/*trans* 88:12, diastereoisomers could not be separated; white solid; m. p. 110°C; *cis* isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.28 (dd, J=7.8, 1.2 Hz, 1H), 7.03 (td, J=7.6, 1.6 Hz, 1H), 6.73 (td, J=7.4, 1.2 Hz, 1H), 6.51 (dd, J=8.0, 0.7 Hz, 1H), 5.11 (d, J=8.0 Hz, 1H), 3.83–3.72 (m, 2H), 3.68 (brs, 1H), 3.03 (dd, J=9.1, 2.7 Hz, 1H), 2.73 (dtd, J=10.4, 8.1, 2.6 Hz, 1H), 2.01 (ddt, J=12.1, 10.3, 8.5 Hz, 1H), 1.85 (ddd, J=8.7, 7.1, 4.2 Hz, 1H), 1.71 (dm, J=9.1, 6.5 Hz, 1H), 1.05 (d, J=6.6 Hz, 3H), 1.00 ppm (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=145.1, 130.0, 128.3, 122.8, 118.8, 114.6, 76.1, 66.7, 59.0, 40.8, 31.3, 24.0, 20.1, 19.2 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{14}H_{20}NO$: 218.154; found: 218.154 $[M+H]^+$.

Ethyl 3a,4,5,9b-tetrahydro(3*H*)cyclopenta[*c*]quinoline-4-carboxylate (5q): Only the *cis* adduct was obtained. Yield: 96%; white solid; m. p. 66°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.98 (m, 2H), 6.71 (td, J=7.5, 1.4 Hz, 1H), 6.63 (dd, J=7.9, 1.2 Hz, 1H), 5.74–5.70 (m, 1H), 5.65–5.63 (m, 1H), 4.69 (brs, 1H), 4.28 (dq, J=27.1, 7.1 Hz, 1H), 4.24 (dq, J=27.1, J=7.1 Hz, 1H), 4.09 (d, J=3.3 Hz, 1H), 4.06 (d, J=2.0 Hz, 1H), 3.33 (qd, J=8.9, 3.5 Hz, 1H), 2.47 (ddq, J=16.0, 8.7, 2.4 Hz, 1H), 2.31 (dddd, J=16.2, 9.0, 2.3, 1.9 Hz, 1H), 1.31 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.1, 144.1, 134.4, 130.0, 128.8, 126.7, 126.2, 119.5, 116.0, 61.4, 56.7, 46.6, 40.9, 32.9, 14.5 ppm; HRMS (ESI, positive mode): m/z: calcd for $C_{15}H_{18}NO_2$: 244.134; found: 244.132 $[M+H]^+$.

Ethyl 2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline-4-carboxylate (5r): Both *cis* and *trans* diastereoisomers were obtained; yield: 97%; *cis*/*trans* 72:28; both products are white solids; *cis* diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.27 (dd, J=7.7, 1.6 Hz, 1H), 7.06 (td, J=7.6, 1.5 Hz, 1H), 6.76 (td, J=7.4, 1.1 Hz, 1H), 6.59 (dd, J=8.1, 1.3 Hz, 1H), 5.19 (d, J=8.1 Hz, 1H), 4.99 (s, 1H), 4.28 (dq, J=20.0, 7.1 Hz, 1H), 4.25 (dq, J=20.0, 7.1 Hz, 1H), 4.18 (d, J=3.3 Hz, 1H), 3.82–3.70 (m, 2H), 3.08 (qd, J=8.8, 3.1 Hz, 1H), 2.04–1.82 (m, 2H), 1.31 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =171.5, 143.7, 130.1, 128.8, 122.3, 119.4, 115.0, 75.7, 66.7, 61.7, 55.5, 40.5, 25.4, 14.4 ppm; *trans* diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.30 (dd, J=7.5, 1.8 Hz, 1H), 7.08 (td, J=7.7, 1.6 Hz, 1H), 6.76 (td, J=7.5, 1.1 Hz, 1H), 6.65 (dd, J=8.1, 0.9 Hz, 1H), 4.60 (d, J=5.9 Hz, 1H), 4.24 (q, J=7.1 Hz, 1H), 4.23 (q, J= 7.1 Hz, 1H), 3.95 (td, J=8.4, 5.6 Hz, 1H), 3.80 (td, J=8.5, 7.1 Hz, 1H), 3.58 (d, J=9.5 Hz, 1H), 2.59 (dddd, J=9.5, 7.8, 5.8, 4.3 Hz, 1H), 2.32–2.13 (m, 2H), 1.29 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.5, 143.3, 130.7, 129.1, 120.3, 119.0, 115.2, 75.2, 65.7, 61.7, 55.7, 39.2, 29.7, 14.4 ppm.

Detailed experimental procedures for **5a–r** and for **4a** and NMR spectra of all new compounds are given in the Supporting Information.

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