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Brønsted and Lewis Solid Acid Catalysts in the Valorization of Citronellal

Federica Zaccheria [1], Federica Santoro [1], Elvina Dhiaul Iftitah [2] and Nicoletta Ravasio [1,*]

[1] CNR Institute of Molecular Science and Technology, Via Golgi 19, 20133 Milano, Italy; f.zaccheria@istm.cnr.it (F.Z.); f.santoro@istm.cnr.it (F.S.)
[2] Chemistry Department Faculty of Science, Brawijaya University Jl. Veteran, Malang 65145, Indonesia; vin_iftitah@ub.ac.id
* Correspondence: n.ravasio@istm.cnr.it; Tel.: +39-02-5031-4382

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Abstract: Terpenes are valuable starting materials for the synthesis of molecules that are of interest to the flavor, fragrance, and pharmaceutical industries. However, most processes involve the use of mineral acids or homogeneous Lewis acid catalysts. Here, we report results obtained in the liquid-phase reaction of citronellal with anilines under heterogeneous catalysis conditions to give tricyclic compounds with interesting pharmacological activity. The terpenic aldehyde could be converted into octahydroacridines with a 92% yield through an intramolecular imino Diels–Alder reaction of the imine initially formed in the presence of an acidic clay such as Montmorillonite KSF. Selectivity to the desired product strongly depended on the acid sites distribution, with Brønsted acids favoring selectivity to octahydroacridine and formation of the *cis* isomer. Pure Lewis acids such as silica–alumina with a very low amount of alumina gave excellent results with electron-rich anilines like toluidine and p-anisidine. This protocol can be applied starting directly from essential oils such as kaffir lime oil, which has a high citronellal content.

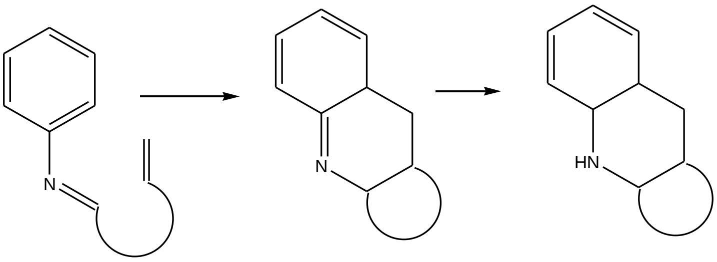
Keywords: solid acids; acidic clays; terpenes; citronellal; octahydroacridines; heterogeneous catalysis

1. Introduction

Terpenes represent a class of natural compounds suited for the synthesis of several types of molecules useful for the industrial production of intermediates for fragrances, flavors, and pharmaceuticals [1]. α-pinene, e.g., one of the main components of turpentine, can be used as a starting material for the synthesis of β-santalol and sandalwood fragrances. These are valuable alternatives to toxic nitro-musks and low-biodegradability polycyclic musks that are among the commonly used fragrances in European laundry detergents, fabric softeners, cleaning agents, and cosmetic products, therefore ubiquitously present in the aquatic environment [2].

In previous years, the use of terpenes has been widely investigated in the polymer industry because of the strong need for renewable and biodegradable materials in this sector [3,4].

Among terpenic molecules, citronellal, citral, limonene, carene, and pinene are common because of their large occurrence in essential oils and in oils derived from agro-industrial residues. Citronellal and citral offer noteworthy opportunities in synthetic strategies because of their condensation and addition reactions by virtue of their unsaturated aldehydic structure. The abundance of these two molecules in essential oils such as kaffir lime, citronella, lemongrass, and krangean oil, promotes their use as raw materials for the sustainable synthesis of different chemicals, specifically N-containing ones. A Schiff base with antibacterial activity was recently synthesized through acid catalysis from citronellal, [5] while benzimidazole derivatives of both aldehydes were obtained by using microwave irradiation [6]. In this case, the aldehyde reacts with *o*-phenylenediamine to give the benzimidazol moiety, but when an aromatic monoamine reacts with an unsaturated aldehyde it gives an N-aryl imine that can further react with the electron-rich alkene moiety through the Povarov reaction, which is an intramolecular imino Diels–Alder reaction [7] (Scheme 1).

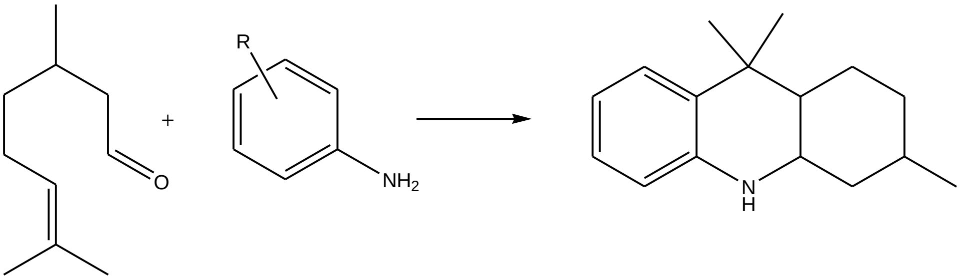


Scheme 1. General intramolecular Povarov reaction.

This class of organic reactions has attracted interest as a useful route of access to N-containing polycyclic structures, such as substituted tetrahydroquinoline and octahydroacridine (OHAs) derivatives. Octahydroacridine systems are an interesting class of biologically active molecules in the field of drugs and pharmaceuticals, acting as gastric acid secretion inhibitors [8] in the prevention of senile dementia [9].

Despite several varying methods available offering access to the octahydroacridine skeleton, such as the Beckmann rearrangement of oxime sulfonate, [10] the catalytic hydrogenation of acridine, [11] and Friedel–Crafts acylation, [12] the simplest one remains the acid catalyzed imino Diels–Alder reaction of 2-azadienes. Because of their poor reactivity in the Povarov reaction, 2-azadienes need to be activated through coordination with acidic catalysts that enhance their electron-deficient character. Both Lewis and Brønsted acids have been used, but, despite their effectiveness, many of these catalysts show disadvantages, such as multistep procedures, long reaction times, use of inert atmosphere, expensiveness, and tedious work-up. Therefore, developing green and efficient catalysts for this reaction is an important challenge.

An efficient synthesis of OHAs starts from citronellal and N-arylamines [13,14] (Scheme 2). This Lewis-acid catalyzed imino Diels–Alder reaction is the most atom-economic way to OHAs, with high yields and, in some cases, high stereoselectivity.

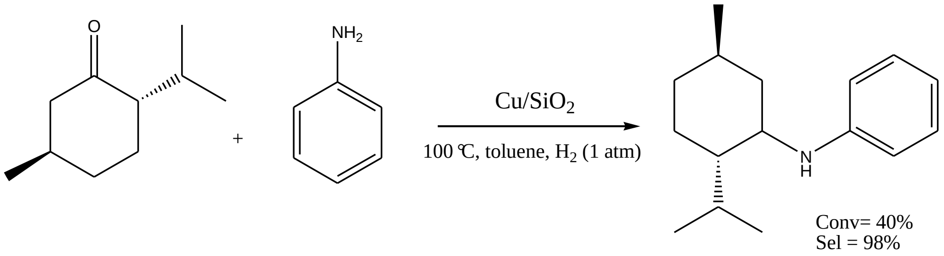


Scheme 2. Reaction of citronellal and anilines into the corresponding octahydroacridine.

During our recent studies on reductive amination of ketones, [15] the attempts to synthesize amine derivatives of C=O-containing terpenes led us to obtain OHAs structures. Herein, we report our results about the synthesis of OHAs from citronellal promoted by solid acid catalysts.

2. Results and Discussion

Previously, we have reported on the use of pre-reduced Cu/SiO_2 (Cu/Si) catalysts in the Direct Reductive Amination (DRA) of aromatic ketones [15]. This is a significant reaction allowing one to obtain secondary amines in one step starting from a ketone, which is still carried out in the presence of unfavorable reagents such as $NaBH_3CN$ or $NaBH(OAc)_3$. The use of a heterogeneous catalyst based on a non-noble metal can yield up to 98% of the amine at 100 °C in a few hours. Unfortunately, under the same conditions, aliphatic terpenic ketones, in particular menthone, a major component of dementholized mint oil, react slowly, requiring a longer time span, although selectivity to the amine is excellent (Scheme 3).



Scheme 3. Amination of menthone with aniline (Conv = Conversion; Sel = Selectivity).

This prompted us to test the reaction of terpenic molecules with a greater number of reactive aldehyde groups.

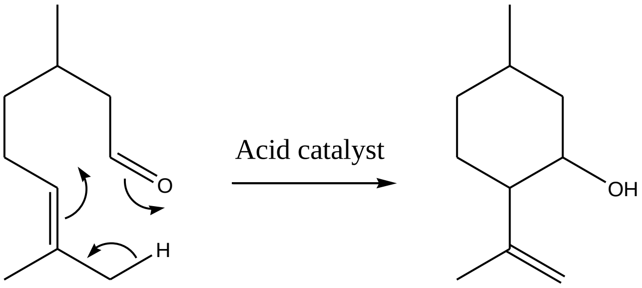
Table 1 reports selected results obtained in the reaction of citronellal under varying conditions and in the presence of several catalytic materials.

Surprisingly, the reaction of citronellal with aniline under DRA conditions, that is, in the presence of pre-reduced Cu catalyst and molecular H_2, was quick and gave the corresponding OHA as the only product in high yield (Table 1, entry 3). A blank test carried out without a catalyst led to the formation of the intermediate imine, without observing the formation of the Diels–Alder product, showing that, in this specific reaction, a catalyst is only necessary for the second step, and a reductive environment is not required (Table 1, entries 1–2). Therefore, both pre-reduction of the catalyst and molecular H_2 could be avoided, and the unreduced CuO/SiO_2 (CuO/Si) catalyst was used at room temperature in the presence of air, giving comparable results.

This reactivity is ascribed to the Lewis acid character of CuO/SiO_2. Thus, the chemisorption–hydrolysis technique used in the preparation of this catalyst allows us to reach a high dispersion of CuO on the silica surface [16]. The CuO particles are small and defective, thus giving an account of the Lewis acidity of this material, able to promote, e.g., the ring opening of epoxides with alcohols [17]. After the reduction pre-treatment, highly defective metal nanoparticles are formed showing Lewis acid activity in a wide range of reactions, particularly in the one-pot production of valeric esters from γ-valerolactone (GVL) and alcohols [18].

Therefore, other solid acids can be used in the synthesis of OHA. Because of our experience in the use of amorphous mixed oxides, we tested some of them in this reaction, namely, a silica–alumina cracking catalyst with a 13% content of Al_2O_3 (SiAl 13) and a 0.6% Alumina on silica (SiAl0.6). Furthermore, we also tested two commercial acid-treated clays, namely, Montmorillonite K10 and KSF. Clays are versatile materials widely used for various applications, including catalytic ones. Thus, increasingly stringent environmental issues and process optimization call for the substitution of liquid acids by more sustainable solid materials. Clays have both Brønsted (B) and Lewis (L) sites, the amount and the strength of which can be modified by acid treatment. Commercial acid-treated clays are widely used industrially as acid catalysts, therefore they are well-defined and reliable materials. K10 is commonly used in the formation of a C–N bond as an alternative to HCl, e.g., in the synthesis of alkylquinolines [19].

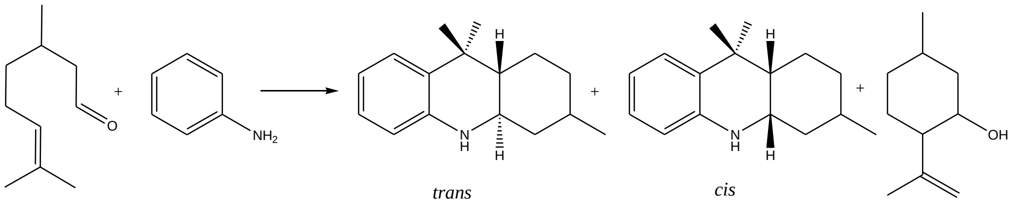
It should be emphasized that, under acidic conditions, citronellal can undergo the *ene* reaction to give isopulegol (Scheme 4). Although this is an interesting reaction, as isopulegol can be hydrogenated to menthol, in the present case this is a secondary reaction that lowers the yield in OHA and, therefore, a fine-tuning of the acidity is mandatory in order to reach a high selectivity to the desired product.



Scheme 4. *Ene* reaction of citronellal into isopulegol.

Results reported in Table 1 show significant differences in selectivity. Considering the reaction between citronellal and aniline, the two amorphous silica–aluminas and Montmorillonite K10 gave a low yield in OHA due to a significant formation of isopulegols (Table 1, entries 6,11,13). This agrees with our previous findings [20], showing that these three catalysts are highly active in the cyclization of citronellal to isopulegol. However, moving from aniline to electron-rich amines, the selectivity to OHA increased, reaching a remarkable 96% yield in the case of p-anisidine over the catalyst with a very low amount of alumina (Table 1, entry 9).

Table 1. Synthesis of octahydroacridines starting from (±)-Citronellal and anilines.



Entry	Catalyst	Amine	Conditions	T h	Conv. %	OHAs Sel %	*Cis/Trans.*	Imine Sel %	Isopulegols %
1	None	aniline	Toluene, 100 °C, N_2	1	73	-	-	87	-
				7.5	96			93	
2	None	aniline	Heptane, 25 °C, air	1	96	-	-	83	-
3	Cu/Si	aniline	Toluene, 100 °C, H_2	1	>99	**97**	37/63	<1	1
4	CuO/Si	aniline	Toluene, 25 °C, air	1	>99	**96**	45/55	-	2
5	CuO/Si	p-anisidine	Toluene, 25 °C, air	1	>99	59	61/39	-	32
6	SiAl 0.6	aniline	Heptane, 25 °C, air	1	>99	71	41/59	<1	24
7	SiAl 0.6	aniline	Heptane, 0 °C, air	1	>99	79	49/51	-	17
8	SiAl 0.6	aniline	Dioxane, 25 °C, air	1	>99	82	58/42	-	14
9	SiAl 0.6	p-anisidine	Heptane, 25 °C, air	1	>99	**96**	51/49	<1	2
10	SiAl 0.6	toluidine	Heptane, 25 °C, N_2	2	>99	90	37/63	-	1
11	SiAl 13	aniline	Heptane, 25 °C, N_2	1	>99	**64**	41/59	-	23
12	SiAl 13	aniline	Heptane, 0 °C, air	1	>99	86	58/42	-	11
13	Mont K10	aniline	Heptane, 25 °C, air	1	>99	**70**	55/45	-	14
14	Mont KSF	aniline	Heptane, 25 °C, air	1	>99	**92**	71/29	-	5
15	Mont KSF	aniline	Heptane, 0 °C, air	1	>99	85	73/27	-	10

It is worth emphasizing that only Lewis acid sites could be detected on the surface of SiAl0.6, as shown by FT IR spectra of adsorbed pyridine, while the other solids used showed also Brønsted acid sites (Table 2). OHA: octahydroacridine.

Table 2. Quantitative determination of acidic sites versus products distribution in the reaction of citronellal with aniline.

Catalyst	Acidic Sites ($mmol_{py/gcat}$)		% OHA	% Cis	% Isopulegols
KSF	0.157	0.025	92	71	5
K10	0.077	0.042	70	55	14
SiAl13	0.039	0.163	64	41	23
SiAl 0.6	-	0.005	71	41	24

Figure 1 shows the comparison of the two amorphous silica–alumina catalysts and the two clays: it is evident that both Brønsted and Lewis sites were present on the surface of the catalyst containing 13% of alumina and on the two clays, whereas the Brønsted ones were absent on the low-loading one.

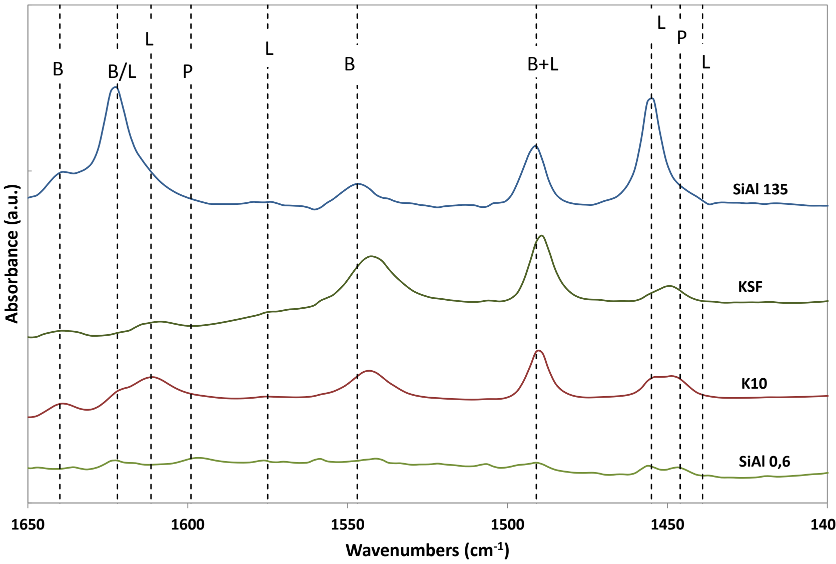


Figure 1. FTIR spectra of pyridine adsorbed on the silica–alumina catalysts: P = physisorbed, B = Brønsted sites, L = Lewis acid sites.

Thus, in SiAl 13, the bands at 1640 cm^{-1}, 1547 cm^{-1}, and 1492 cm^{-1} are the intense modes of pyridinium cations associated with a total proton transfer from the Brønsted acidic surface OH group to the basic molecule, whereas the bands at 1623 cm^{-1} and 1455 cm^{-1} are due to the pyridine molecularly coordinated on Al^{3+} cations, acting as Lewis acid sites [21].

However, the spectra of pyridine adsorbed on clays, KSF, and K10, showed the presence of both Lewis and Brønsted sites, although the former in lower concentration.

The presence of weak absorption bands at 1545 cm^{-1}, 1490 cm^{-1}, and 1450 cm^{-1}, indicating the presence of both Brønsted and Lewis acidity in low concentrations, has already been reported, although in the Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectra of pyridine adsorbed on the surface of montmorillonite K10 [22], while the presence of medium-weak Brønsted sites and strong Lewis sites was evidenced by a range of complementary experimental techniques by Lenarda et al. [23]. However, the number of these sites has never been quantified. Table 2 shows that B sites in KSF are twice the number of those in SiAl 13, that in turn are twice the number of those in K10, in agreement with previous determinations through NH_3 chemisorption of acidic sites in KSF and K10 [24].

Comparing the results obtained with the relative number of acidic sites reported in Table 2, it is apparent that, for catalysts containing both B and L sites, the yield in OHA increases with the number of B sites, while the amount of isopulegols increases with the number of L sites (Figure 2).

The catalyst that contains only L sites showed an intermediate behavior, giving only 71% of OHA in the reaction of citronellal and aniline (Table 1, entry 6). However, by increasing the electro-donor ability of the substituent, this catalyst gave excellent results, reaching a 96% yield in the reaction with anisidine (Table 1, entry 9).

According to our results, differences in acidity can also influence products stereochemistry.

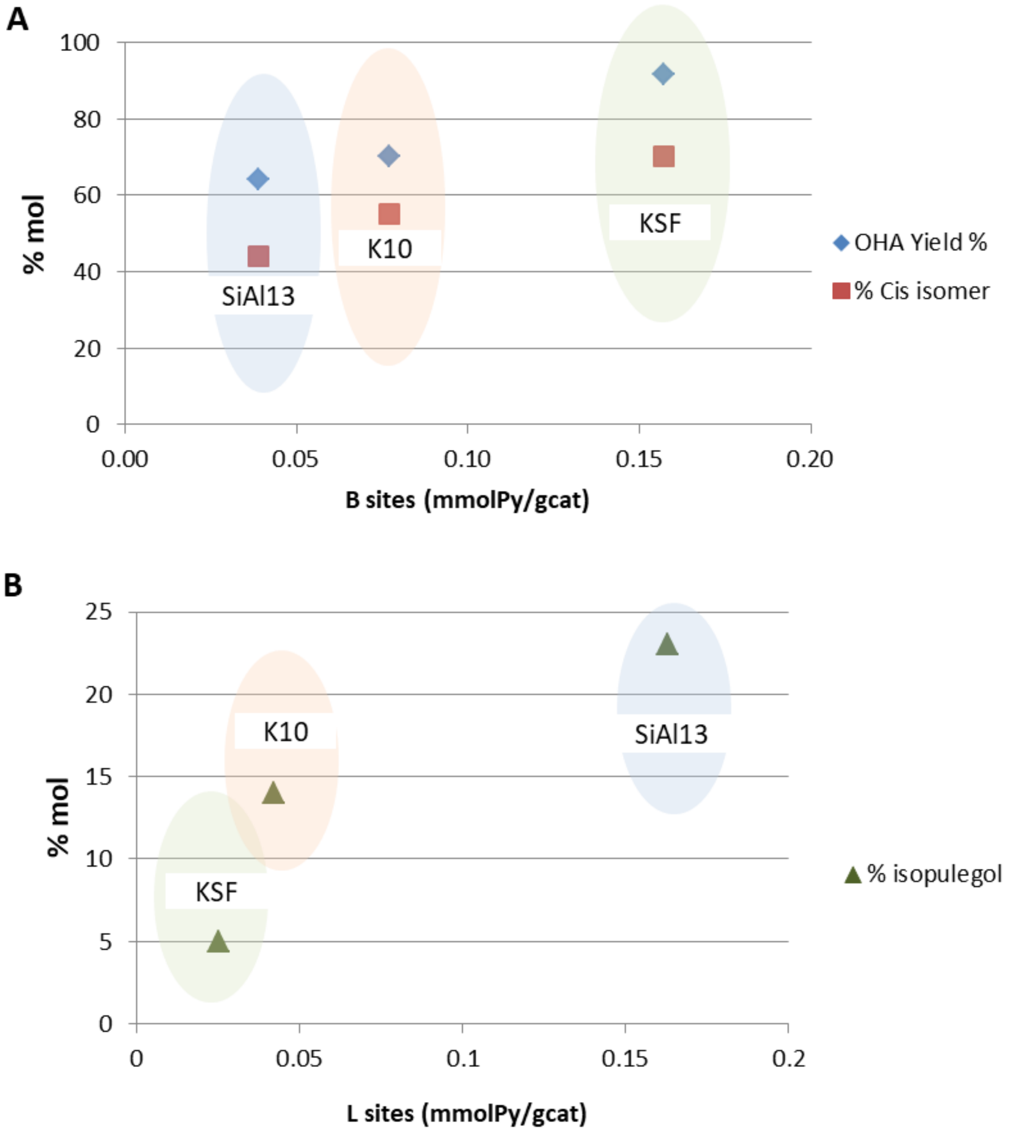


Figure 2. Trend in products distribution versus the concentration of B acidic sites (**A**) and L sites (**B**).

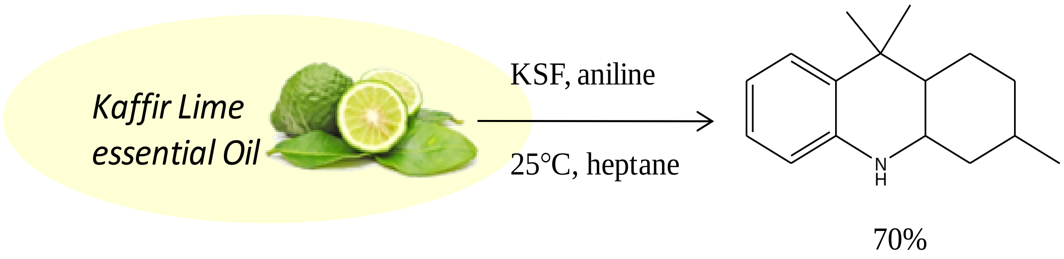
Laschat and Lauterwein [25] reported on the use of several homogeneous Lewis acids at −78 °C in CH_2Cl_2 and drew the conclusion that the catalyst plays only a minor role in determining the *cis/trans* ratio. In agreement with this work, Kouznetsov [26] found that the bulkiness of the aniline derivative has a pivotal role when both Lewis and Brønsted acids are used as a catalyst, allowing to reach 97% of the *trans* isomer for the N-benzyl-aniline derivative at room temperature. However, in the presence of $TiCl_3$, the *cis/trans* ratio did not change significantly by changing the amine [9].

Reports on heterogeneous catalysts in this specific reaction are rare; $ZnCl_2$ supported on silica was used in the presence of microwaves, giving a 78% yield in the case of aniline, with a *cis/trans* ratio of 1:1 [13]. The introduction of electron-donor or electron-withdrawer substituents on the aniline moiety influenced both yield and stereochemistry of the products.

In the present case, differences in stereochemistry are evident. Specifically, pure Lewis solids (both CuO/silica and SiAl 0.6) promote 40/60 mixtures with a slight excess of *trans* isomers. When introducing B acid sites, the number of *cis* isomers increases, and the solid with a more prominent B acid character, namely, KSF, favors the formation of the *cis*-isomer (Table 1, entries 14 and 15, Figure 2A). This could be because of the different adsorption of the intermediate imine on the catalyst surface, with Brønsted sites binding strongly to the N atom and favoring the transition state leading to the *cis* isomer.

The solid catalyst is also reusable, allowing to obtain the desired OHA product, although in lower yield (75%) under non-optimized conditions, such as without washing the catalyst.

This protocol can be successfully applied directly to essential oils. Thus, the reaction of kaffir lime oil with aniline in heptane and in the presence of clay KSF produced an oil containing 70% of octahydroacridine in one hour (Scheme 5).



Scheme 5. Octahydroacridine formation, starting directly from kaffir lime.

3. Experimental Section

3.1. Materials and Methods

(±)-Citronellal (>95%), aniline (>99%), *p*-anisidine (>99%) and toluidine (99%) were purchased from Sigma-Aldrich (Milan, Italy) and used without pretreatment. Kaffir lime (*Citrus hystrix D.C*) oil was obtained from the Essential Oil's Institute Atsiri, Brawijaya University, Malang (RI).

SiO_2–Al_2O_3 13 (Surface Area = 485 m^2/g, Pore Volume = 0.79 mL/g), was purchased from Sigma-Aldrich; SiO_2–Al_2O_3 0.6 (Surface Area = 483 m^2/g, Pore Volume = 1.43 mL/g) was kindly provided by GRACE Davison. Montmorillonite KSF and Montmorillonite K10 were purchased from Sigma-Aldrich; SiO_2 (Surface Area = 460 m^2/g, Pore Volume = 0.74 mL/g) was purchased from Fluka (Milan, Italy).

3.2. Copper Catalyst Preparation

CuO/SiO_2 (with 16% of copper loading) catalyst was prepared by the chemisorption–hydrolysis technique as reported [16], by adding the support to an aqueous $[Cu(NH_3)_4]^{2+}$ solution prepared by dropping NH_4OH into a $Cu(NO_3)_2 \cdot 3H_2O$ solution until pH 9 had been reached. After 20 min under stirring, the slurry, held in an ice bath at 0 °C, was diluted with water. The solid was separated by filtration with a Büchner funnel, washed with water, dried overnight at 120 °C, and calcined in air at 350 °C.

3.3. Catalyst Characterization

FTIR Spectra of adsorbed pyridine. The FT-IR studies of probe molecules (pyridine) adsorption and desorption were carried out with a BioRad FTS-60 (Segrate, Italy) spectrophotometer equipped with a mid-IR MCT detector. The experiments were performed on a sample disk (15–20 mg) after a simple calcination treatment (180 °C, 20 min air + 20 min under vacuum). One spectrum was collected before probe molecule adsorption as a blank experiment. Therefore, pyridine adsorption was carried out at room temperature, and the following desorption steps were performed from room temperature to 250 °C. The spectrum of each desorption step was acquired every 50 °C after cooling the sample. For quantitative analysis, the amount of adsorbed pyridine ($mmol_{Py}/g_{cat}$) was calculated on the basis of the relationship reported by Emeis [27] from the integration of diagnostic bands evaluated in the spectra registered at 150 °C.

3.4. Catalytic Tests

Prior to the catalytic tests, the catalysts (100 mg) were pretreated as follows: SiO_2–Al_2O_3 was calcined for 20 min in air at 180 °C and 20 min under vacuum at the same temperature; Montmorillonite

KSF and Montmorillonite K10 were dried in an oven at 120 °C for one night; CuO/SiO_2 was calcined for 20 min in air at 270 °C and 20 min under vacuum at the same temperature, and a following reduction step with H_2 (1 atm) was performed for Cu/SiO_2-catalyzed reactions.

In a glass reaction vessel containing the pretreated catalyst, a mixture of citronellal (0.55 mmol) and amine (1.66 mmol) in 5 mL of solvent was charged. Therefore, the reaction proceeded with the proper temperature conditions under magnetic stirring. At the desired reaction time, the mixture was separated by simple filtration from the catalysts, and the products were analyzed by GC–MS (5%-phenyl-methyl polysiloxane column) and NMR (Bruker 500 MHz).

For the recycling tests, the solution was separated from the catalyst after the first run by simple decantation, and a fresh reaction mixture was charged in the reactor without treating the catalyst.

In the experiment carried out with Kaffir lime oil, a mixture containing 100 µL of essential oil and 1.66 mmol of aniline in 5 mL of solvent was charged in a glass reaction vessel containing 100 mg of KSF dried overnight at 120°C.

^{1}HNMR data (300 MHz, $CDCl_3$) (See Supplementary Materials for NMR Spectra) A) *cis* isomer: δ = 0.98 (d, J = 6.4, 3 H, CH_3), 1.07–1.89 (m, 2H, CH_2), 1.13–1.97 (m, 2H, CH_2), 1.31 (s, 3H, CH_3), 1.33 (s, 1 H, CH), 1.38 (s, 1 H, CH), 1.41 (s, 3H, CH_3), 1.83 (m, 1H, CH), 1.86 (m, 1H, CH), 3.69 (bs, NH), 3.92 (dt, 1H, CH), 6.51 (dd, 1H, CH), 6.68 (m, 1H, CH), 7.04 (m, 1H, CH), 7.22 (dd, 1H, CH).

MS (EI): m/z (%) = 229.2 (34), 214.2 (100), 158.1 (12), 144.1 (29).

B) *trans* isomer: 0.99–1.77 (m, 2H, CH_2), (d, J = 6.5, 3H, CH_3), 1.13 (m, 1H, CH), 1.19 (s, 3H, CH_3), 1.33–1.83 (m, 2H, CH_2), 1.40 (m, 1H, CH), 1.42 (s, 3H, CH_3), 1.97 (m, 1H, CH), 3.16 (dt, 1H, CH), 3.69 (bs, NH), 6.52 (dd, 1H, CH), 6.73 (s, 1H, CH), 7.04 (m, 1H, CH), 7.04 (m, 1H, CH), 7.31 (dd, 1H, CH).

MS (EI): m/z (%) = 229.2 (55), 214.2 (100), 158.1 (18), 144.1 (33).

4. Conclusions

The introduction of solid acid materials in organic synthesis is an ambitious target of green chemistry. Thus, a heterogeneous catalyst could be filtered off at the end of the reaction without the need of a neutralization step followed by washing and the time-consuming workup of the reaction mixture producing significant amounts of inorganic salts. N-containing heterocycles are the most abundant class of compounds synthesized by the pharmaceutical industry [28]. Here, we show that very simple inorganic materials such as Montmorillonite, that is a natural acidic clay, can effectively promote the synthesis of N-containing octahydroacridines with a 92% yield in one hour and at room temperature, starting from anilines and citronellal, the main component of several essential oils. In some cases, yields were almost quantitative due to high selectivity with respect to the competing *ene*-reaction to isopulegols. Both high selectivity and the use of solid acid catalyst allowed us to obtain a negligible waste process, showing high sustainability.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/8/10/410/s1, Figure S1: ^{1}HNMR of octahydroacridine obtained from citronellal and aniline.

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Conflicts of Interest: The authors declare no conflict of interest.

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