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FULL PAPER

Revisiting the Betti synthesis: using a cheap, readily-available, recyclable clay catalyst in solventless conditions

Giovanna Bosica*[a], Roderick Abdilla,[a] and Kaylie Demanuele[a]

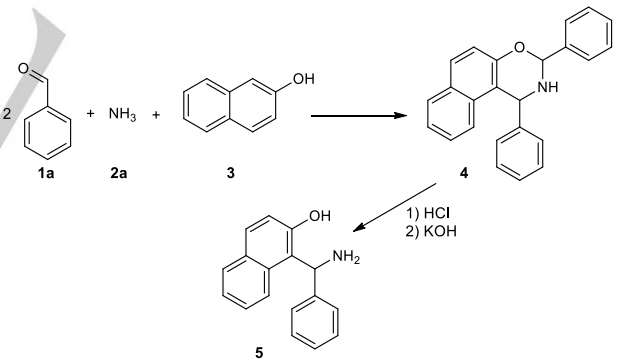
Abstract: One-pot multicomponent reactions have gained significant importance in recent years because they are usually more selective, simple, efficient, atom-economic and green than their multistep counterparts. The Betti synthesis involves the combination of aldehydes, amines and 2-naphthol to form compounds which can serve as catalysts or as biologically active compounds. In this study, Montmorillonite K30 was used as a heterogeneous catalyst for the Betti reaction at 60 ^{0}C in relatively short reaction times. Positively, it is cheap, readily and commercially available and requires no preparation, it can be used in neat conditions whilst minimizing excess reagent amounts. Most importantly, it is fully recoverable and can be recycled up to 5 times. In reactions involving secondary aliphatic amines, very good to excellent results were obtained whilst primary ones including benzylamine gave appreciable yields. In addition, the heteroaromatic aldehyde 4-pyridinecarboxaldehyde and the polyaromatic aldehyde 1-naphthaldehyde also gave encouraging results.

Introduction

Over the past few years most of our studies have focused on one-pot multicomponent reactions (MCRs) because of the significant advantages they offer over conventional multistep synthesis including: selectivity, atom-economy, simplicity, shorter reaction times and environmental benignity.[1] The earliest MCR which was discovered was the Strecker (1850) synthesis and along with it there are several other tried and tested classical ones including: the Biginelli (1891), Hantzsch (1882), Mannich (1912), Passerini (1921) and the Ugi (1959) reactions.[1] However, organic chemists have used various rational methods in order to develop new MCRs to build novel chemical libraries. Amongst such methods, the single reactant replacement (SRR) technique involves replacing one of the reactants by a related one which can have a similar role in the overall mechanism of the reaction.[2] For example, whereas the Mannich reaction is classically a combination of an aldehyde, an amine and a carbonyl compound which acts as a nucleophile for the imine formed between the aldehyde and the amine, the carbonyl compound can be replaced by an alkyne in the A^3-coupling, by a nitro compound in the nitro-Mannich reaction, by an indole in the aza-Friedel-Crafts reaction or by a naphthol in the case of the Betti synthesis.[3-6]

Originally, the Betti reaction involved a three component condensation of two equivalents of benzaldehyde (**1a**), one equivalent of ethanolic ammonia (**2a**) and one equivalent of 2-naphthol (**3**) to give **4** which is identified as 1,3-diphenyl-2,3-dihydro-1H-naphth[1,2-e][1,3]oxazine.[6] Treatment of **4** by hydrochloric acid followed by potassium hydroxide yielded 1-(α-aminobenzyl)-2-naphthol which is also called the Betti base (**5**) (**Scheme 1**). With time this reaction was modified by replacing ammonia with alkyl or aryl amines and various catalysts were developed in order to improve the yield of theses reactions.[7]

Betti bases have several uses including catalytic and biological ones. With regards to the former use, the condensation of 2-naphthol, benzaldehyde and (*S*)-methylbenzylamine followed by *N*-methylation was discovered to catalyze the enantioselective ethylation of aryl aldehydes to secondary alcohols.[8]



Scheme 1. The original Betti reaction between benzaldehyde (**1a**), ammonia (**2a**) and 2-naphthol (**3**) to yield **4** before treating with HCl and KOH to ultimately form the Betti base (**5**).

Meanwhile, various products synthesized using morpholine or *N,N*-dimethylamine instead of ammonia were tested as analgesic agents because of their affinity towards α-adrenergic and opioid receptors.[9] More importantly, the hydroxyl group in Betti bases can be exploited to form compounds which have several biological applications such as antibacterial, hypotensive and bradycardiac activities[10,11] in fact one of the most important areas of application of these aminonaphtol derivatives is the synthesis of new heterocycles.[12]

Focusing on the reaction between aldehydes, amines and 2-naphthol, both homogeneous and heterogeneous catalysts were

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employed to varying success. In earlier studies, the former type of catalysts were used including lithium perchlorate in diethyl ether solvent, *p*-toluenesulfonic acid (TSA) under microwave radiation, DMEA organocatalyst in neat conditions, Triton X-100 surfactant in water etc.[13-16] Furthermore, in two separate studies, an ionic liquid and polyethylene glycol (PEG) were utilized because they serve as catalysts and solvents simultaneously.[17,18] However, all of these catalysts cannot be reused or recycled easily and suffer from one or more of the following disadvantages: they need to be used in a solvent, are expensive and have short-term stability.

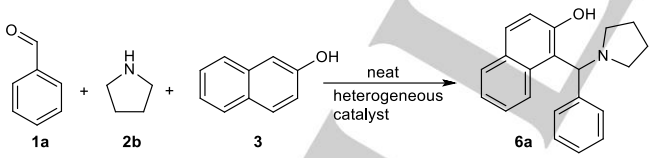
Conversely, heterogeneous catalysts can be usually reused and recycled and studies involving nano-magnesium oxide, nano-magnetite, nano-titania-perchloric acid and nano-silica-boric acid were greener because they gave excellent yields in short reaction times usually in neat conditions.[19-22] Yet, nano-catalysts are more difficult and expensive to prepare, more problematic to separate from the crude reaction mixture (centrifugation) whilst the latter catalysts involve the use of the highly corrosive and non-environmentally benign perchloric acid and boric acid respectively. Henceforth, in continuation of our research on new synthetic methods in organic synthesis using heterogeneous catalysts, we developed a multicomponent Betti synthesis employing a metal-free, clay catalyst, Montmorillonite K30, which is specifically a phyllosilicate, and has the following advantages amongst others (as will be discussed later on):

- Cheap and readily and commercially available
- Requires no preparation
- Easily recyclable and reusable
- Metal free (no leaching is possible)

Results and Discussion

Catalyst screening and condition optimization

Prior to identifying MK30 as the ideal catalyst for substrate screening, various other catalysts were tested for the model reaction shown in **Scheme 2**.



Scheme 2. Model reaction between benzaldehyde (**1a**), pyrrolidine (**2b**) and 2-naphthol (**3**) to form **6a**.

When heterogeneous Brønsted acids were initially tested (**Table 1**, **entries 1 – 5**) the yields were not very interesting whilst when metal/non-metal oxides were used results were no better except for the case of acidic alumina (**entries 6 and 7**). The use of phyllosilicate catalysts Montmorillonite K10 and Montmorillonite K30 (**entries 11 – 14**) caused an upshift in yields especially on using them after drying for 24 hours in an oven set at 130 ^{0}C. Lewis acid exchanged Montmorillonite K10 catalysts did not give better results. In conclusion, activated Montmorillonite K30 was chosen because it gave the best result of 81% (**entry 14**).

Table 1. Catalyst screening for the model reaction involving benzaldehyde (**1a**), pyrrolidine (**2b**) and 2-naphthol (**3a**).

Entry[a]	Catalyst	Amount of catalyst (mol% or g)	Yield[b] (%)
1	Methanesulfonic acid – alumina (0.5 mmol/g)[c]	10 mol%	42
2	Amberlyst 15	0.3 g	26
3	Silicotungstic acid / Amberlyst 15 (30% w/w)[d]	0.3 g	41
4	Silicotungstic acid / Montmorillonite K10 (20% w/w)[e]	0.3 g	63
5	Perchloric acid – cellulose (0.5 mmol/g)[f]	5 mol%	66
6	acidic alumina[g]	0.3 g	66
7	Activated acidic alumina[h]	0.3 g	77
8	Neutral activated alumina[h]	0.3 g	22
9	Silica[g]	0.3 g	39
10	Zirconium (IV) oxide[g]	0.3 g	55
11	Montmorillonite K10[g]	0.3 g	73
12	Activated Montmorillonite K10[h]	0.3 g	78
13	Montmorillonite K30[g]	0.3 g	75
14	Activated Montmorillonite K30[h]	0.3 g	81
15	4A Molecular sieves[g]	0.3 g	33
16	Copper(I) iodide – alumina[i]	10 mol%	62
17	Copper(I) iodide – Amberlyst A21[i]	10 mol%	0
18	Copper(II)-Montmorillonite K10[k]	0.3 g	68
19	Iron(III)-Montmorillonite K10[k]	0.3 g	63
20	Aluminium(III) – Montmorillonite K10[k]	0.3 g	69
21	Zinc (II) – Montmorillonite K10[k]	0.3 g	36

[a] All reactions were performed at room temperature for 24 hours in neat conditions with the reactants (benzaldehyde (**1a**) / pyrrolidine (**2b**) / 2-naphthol (**3**)) in the molar ratio of 1.2 : 1 : 1 at a scale of 2.5 mmol. [b] Pure isolated yield after column chromatography and recrystallization from ethanol. [c] Catalyst was prepared according to method reported in [23]. [d] Catalyst was prepared according to method reported in [24]. [e] Catalyst was prepared according to method reported in [25]. [f] Catalyst was prepared according to method reported in [26]. [g] Catalyst was used as bought and was not dried. [h] Catalyst was dried at 130 ^{0}C for 24 hours before use. [i]

Catalyst was prepared according to method reported in [27]. [j] Catalyst was prepared according to method reported in [28]. [k] Catalyst was prepared according to method reported in [29].

Subsequently, condition optimization was performed by initially varying the amount of catalyst (**Table 2**). Decreasing the amount proved detrimental whilst increasing it caused the reaction to dry out completely and a significant amount of diethyl ether would have had to be added to ensure stirring, something which is not environmentally benign (**entries 2, 3**). Conversely, using the original amount of catalyst whilst increasing the amine excess, caused a positive change in the yield (**entry 4**).

The last few trials (**entries 5 – 8**) involved carrying out the reaction at a higher temperature of 60 ^{0}C and impressively reaction times decreased to 3 hours. More importantly, when the reactant ratio between benzaldehyde (**1a**), pyrrolidine (**2b**) and 2-naphthol (**3**) was 1.2 : 1.5 : 1, both activated and unactivated MK30 yielded identical results (**entries 7 – 8**). Finally, when the ratio was changed to 1.1 : 1.2 : 1 and unactivated MK30 was used (**entry 9**), a yield of 91% was obtained meaning that the latter conditions had to be chosen because they would result in a more energy-efficient and green procedure.

Table 2. Condition optimization for model Betti reaction using Montmorillonite K30 as the catalyst of choice.

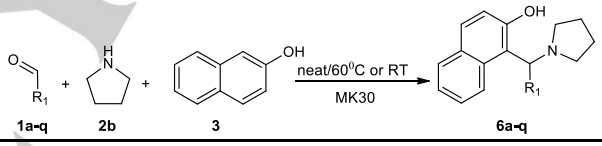
Entry[a]	Catalyst	Catalyst Amount	Reactant ratio[b]	T (^{0}C)	Yield[c] (%) [Time] (hours)
1	Activated MK30[d]	0.3 g	1.2 : 1 : 1	RT	81 [24]
2		0.2 g	1.2 : 1 : 1	RT	56 [24]
3		0.4 g	1.2 : 1 : 1	RT	/[e]
4		0.3 g	1.2 : 1.5 : 1	RT	86 [24]
5	Unactivated MK30[f]	0.3 g	1.2 : 1.1 : 1	60	78 [3]
6	Activated MK30[d]	0.3 g	1.2 : 1.1 : 1	60	84 [3]
7	Unactivated MK30[f]	0.3 g	1.2 : 1.5 : 1	60	90 [3]
8	Activated MK30[d]	0.3 g	1.2 : 1.5 : 1	60	90 [3]
9	Unactivated MK30[f]	0.3 g	1.1 : 1.2 : 1	60	91 [3]

[a] All reactions were performed on a 2.5 mmol scale using activated or unactivated MK30. [b] Molar ratio of benzaldehyde (**1a**), pyrrolidine (**2b**) and 2-naphthol (**3**). [c] Pure isolated yield following column chromatography and recrystallization from ethanol. [d] Montmorillonite K30 was dried at 130 ^{0}C for 24 hours. [e] Reaction dried out immediately and a lot of solvent would have had to be required to ensure stirring, something which is not environmentally-benign. [f] Montmorillonite K30 was used directly as bought.

Substrate screening: using pyrrolidine

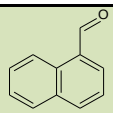
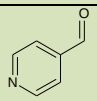
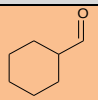
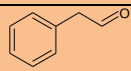
In the initial stages of substrate screening (**Table 3**), a wide range of aldehydes were reacted with pyrrolidine (**2b**) and 2-naphthol (**3**). Furthermore, in order to highlight further the difference the increase in temperature made, most reactions were performed under both the ideal conditions established at room temperature and at 60 ^{0}C. At the latter conditions, very good to excellent yields (79 – 92%) were usually obtained in a maximum of 6 hours for several different aldehydes with the exception of 4-fluorobenzaldehyde (50%), probably owing to its photo and thermal instability, and 2-methoxybenzaldehyde (60%) probably due to steric hindrance. Understandably, the electron rich methoxybenzaldehydes (**entries 3 – 5**) gave lower results than the electron poor cyano- and nitrobenzaldehydes (**entries 7 – 8**). Regrettably, aliphatic aldehydes gave several products each of which was very small in amount and could not be identified (**entries 15 – 17**). Positively, the polyaromatic aldehyde 1-naphthaldehyde gave a very good result (**entry 9**) as did the heteroaromatic aldehyde 4-pyridinecarboxaldehyde (**entry 10**) the latter of which, to the best of our knowledge, has never been employed.

Table 3. Yields and reaction times for the reactions involving aldehydes (**1a - q**), pyrrolidine (**2b**) and 2-naphthol (**3**) at room temperature and at 60 ^{0}C.



1a-q 2b 3 6a-q

Entry	R^1 or 1	Yield (%)[a] at RT[b] [Time (hrs)]	Yield (%)[a] at 60 ^{0}C[c] [Time (hrs)]	
1* (model reaction)	C_6H_5 (**1a**)	86 [7]	91 [3] (**6a**)	
2	4-CH_3-C_6H_4 (**1b**)	83 [7]	90 [3] (**6b**)	
3	2-OCH_3-C_6H_4 (**1c**)	51 [24]	60 [6] (**6c**)	
4	3-OCH_3-C_6H_4 (**1d**)	72 [24]	81 [3] (**6d**)	
5	4-OCH_3-C_6H_4 (**1e**)	48 [12]	83 [2] (**6e**)	
6	2-NO_2-C_6H_4 (**1f**)	0 [24]	0 [6] (**6f**)	
7	4-NO_2-C_6H_4 (**1g**)	90 [4]	92 [2] (**6g**)	
8	4-CN-C_6H_4 (**1h**)	91[4]	92 [2] (**6h**)	

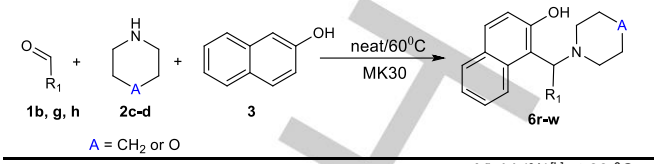
9	 (**1i**)	70 [24]	79 [6] (**6i**)
10	 (**1j**)	70 [24]	74 [6] (**6j**)
11	4-F-C_6H_4- (**1k**)	37 [24]	50 [6] (**6k**)
12	4-Cl-C_6H_4- (**1l**)	75 [24]	83 [2] (**6l**)
13	4-Br-C_6H_4- (**1m**)	79 [24]	84 [2] (**6m**)
14	3,4-Cl_2-C_6H_3 (**1n**)	59 [12]	86 [5] (**6n**)
15	 (**1o**)	0 [24]	0 [3] (**6o**)
16	 (**1p**)	0 [24]	0 [6] (**6p**)
17	$CH_3(CH_2)_3CHO$ (**1q**)	0 [24]	0 [4] (**6q**)

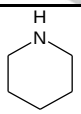
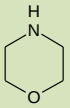
[a] Pure isolated yield following column chromatography and recrystallization from ethanol. [b] Reactions were performed on a 2.5 mmol scale using a molar ratio of aldehyde (**1a-q**), pyrrolidine (**2b**) and 2-naphthol (**3**) of 1.2 : 1.5 : 1 at room temperature in neat conditions in the presence of 0.3g activated MK30. [c] Reactions were performed on a 2.5 mmol scale using a molar ratio of aldehyde (**1a-q**), pyrrolidine (**2b**) and 2-naphthol (**3**) of 1.1 : 1.2 : 1 at 60 ^{0}C in neat conditions in the presence of 0.3 g unactivated MK30.

Substrate screening: using other secondary aliphatic amines and primary amines

The use of either piperidine (**2c**) or morpholine (**2d**) instead of pyrrolidine (**2b**) yielded excellent results (**Table 4**) although it must be noted that the reaction times increased to a significant extent (up to 12 hours) when compared to those involving pyrrolidine.

Table 4. Yields and reaction times for the reactions involving aldehydes (**1b**, **g**, **h**), piperidine/morpholine (**2c**-**d**) and 2-naphthol (**3**) at 60 ^{0}C.

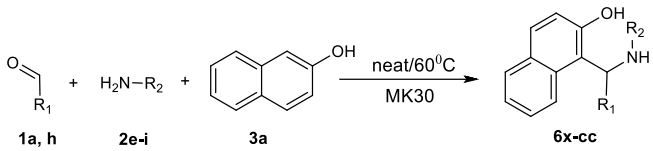


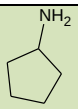
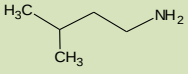
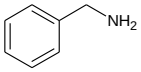
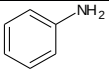
Entry[a]	R^1	Amine	Yield (%)[b] at 60 ^{0}C [Time (hrs)]
1	4-CH_3-C_6H_4 (**1b**)	 (**2c**)	87 [10] (**6r**)
2	4-NO_2-C_6H_4 (**1g**)	**2c**	76 [12] (**6s**)
3	4-CN-C_6H_4 (**1h**)	**2c**	90 [4] (**6t**)
4	**1b**	 (**2d**)	86 [12] (**6u**)
5	**1g**	**2d**	78 [12] (**6v**)
6	**1h**	**2d**	84 [12] (**6w**)

[a] Reactions were performed on a 2.5 mmol scale using a molar ratio of aldehyde (**1b**/**g**/**h**), piperidine/morpholine (**2c**/**d**) and 2-naphthol (**3**) of 1.1 : 1.2 : 1 at 60 ^{0}C in neat conditions in the presence of 0.3 g inactivated MK30. [b] Pure isolated yield following column chromatography and recrystallization from ethanolTable Footnote.

Turning onto the aliphatic primary amines (**Table 5**), products were obtained in varying yields (37 – 80%) with the lower ones being obtained by cyclopentylamine and isopentylamine and the highest obtained using the linear *n*-butylamine (**entries 1 - 3**). Interestingly, benzylamine gave appreciable results (**entries 4, 5**) which, to the best of our knowledge, have never been obtained under neat heterogeneous conditions. On the other hand aniline did not give any product owing to its relative lack of reactivity.

Table 5. Yields and reaction times for the reactions involving aldehydes (**1a**,**h**), primary amines (**2e** – **i**) and 2-naphthol (**3a**) at 60 ^{0}C.



Entry [a]	R^1 or 1	Amine (**2e-i**)	Yield (%)[b] at 60 ^{0}C [Time (hrs)]
1	C_6H_5- (**1a**)	$CH_3(CH_2)_3NH_2$ (**2e**)	80 [12] (**6x**)
2	**1a**	 (**2f**)	38 [12] (**6y**)
3	**1a**	 (**2g**)	38 [12] (**6z**)
4	**1a**	 (**2h**)	66 [12] (**6aa**)
5	4-CN-C_6H_4- (**1h**)	**2h**	37 [12] (**6bb**)
6	**1b**	 (**2i**)	0 [30] (**6cc**)

[a] Reactions were performed on a 2.5 mmol scale using a molar ratio of aldehyde (**1a/h**), amine (**2e-i**) and 2-naphthol (**3**) of 1.1 : 1.2 : 1 at 60 ^{0}C in neat conditions in the presence of 0.3g inactivated MK30. [b] Pure isolated yield following column chromatography and recrystallization from ethanol.

Interestingly during ^{13}C-NMR spectroscopy characterization we found that all products having heterocyclic amines had a similar trend for the amine ring portion, showing two broad peaks for the -CH_2NCH_2- carbons and so one carbon more in count.[12b] Performing a temperature study on sample **6w** we observed that these two broad peaks become a single one at higher temperatures (**Figure 1**), indicating a restricted rotation at room temperature.

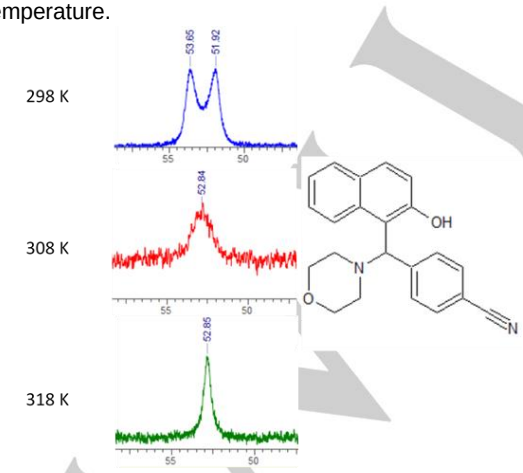


Figure 1. Temperature study on ^{13}C-NMR spectroscopy for compound (**6w**).

Recycling test

When the model reaction involving the synthesis of **6a** from **1a, 2b** and **3** was repeated after filtering and reusing the catalyst, it was found out that the latter could be reused for up to five times with the yield decreasing from 91% to 80% (**Figure 2**). Considering that all reactions were allowed to take place for the same amount of time (i.e. 7 hours), the results show only a slight loss of activity of the catalyst, according to the small decrease of the yields obtained. Between each trial, the catalyst was left to dry in an oven at 130 ^{0}C overnight in order to remove any solvent and moisture adsorbed onto it during the reaction.

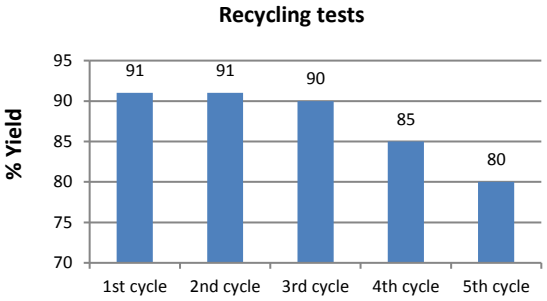


Figure 2. Yields of recycling trials.

Green metrics

The "greenness" of a reaction can be approximately quantified by calculating both the *E-factor* and the *atom economy* amongst other factors. For the model reaction, involving **1a, 2b** and **3**, the *atom economy* is equal to:

$$Atom\ economy = \frac{RMM_{product}}{\sum RMM_{starting\ materials}} * 100\% = \frac{303.40}{144.16 + 106.12 + 71.12} * 100\% = 94\%$$

Meanwhile, the *E-factor* for the same reaction is equal to:

$$E - factor = \frac{total\ mass\ of\ product}{total\ mass\ of\ waste} = \frac{91\% * 0.00250 * 303.40}{(0.00250 * 144.16) + (0.00275 * 106.12) + (0.003 * 71.12) - 91\% * 0.00250 * 303.40} = 3.92$$

The one-pot multicomponent approach, using commercially available non-hazardous starting materials, displays a 'green' protocol with a high atom economy and low E-factor.

Conclusions

The one-pot multicomponent Betti synthesis was performed under green heterogeneous and neat conditions in the presence of Montmorillonite K30 catalyst which is safe, cheap, readily available and does not require any preparations. It is fully recoverable and recyclable for up to 5 runs. Furthermore, it could catalyse reactions involving both secondary and primary aliphatic

amines to give products usually in good to excellent yields. In addition, to the best of our knowledge this is the first time that benzylamine could be used in neat heterogeneous conditions whose products have immense potential. The developed protocol displays both a very high Atom Economy as well as a low E-Factor.

Experimental Section

Methodology

General

All commercially available chemicals were purchased from Aldrich and used without further purification. IR spectra were recorded on a Shimadzu IR Affinity-1 FTIR spectrometer calibrated against a 1602 cm^{-1} polystyrene absorbance spectra. Samples were analysed as thin films in between sodium chloride discs. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD® NMR spectrometer, equipped with an Ascend 500 11.75 Tesla superconducting magnet, operating at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C, and a multinuclear 5 mm PABBO probe. Samples were dissolved in deuterated chloroform (with TMS). Mass spectra were performed using a Waters® ACQUITY® TQD UPLC/MS/MS system equipped with the Atmospheric Solids Analysis Probe (ASAP). Melting points of products were measured using a Stuart® SMP11 melting point determination apparatus fitted with a mercury thermometer. Reactions were monitored using TLC plates composed of silica on PET with fluorescent indicator. Plates were observed under a UV lamp at a wavelength of 254 nm before staining in an iodine-saturated chamber.

Overall method

The general procedure for the Betti reaction involved stirring the aldehyde (2.75 mmol), the amine (3.00 mmol) and the 2-naphthol (2.50 mmol) until the latter dissolved. Then, Montmorillonite K30 catalyst (0.30 g) was carefully added via a plastic funnel before the reaction mixture was allowed to stir under neat conditions in a nitrogen-dried 10 mL two-necked round-bottomed flask fitted with a reflux condenser and heated in an oil bath set at 60 ^{0}C. Often times, reaction mixture thickened completely after 1-2 hours of mixing and hence about 4 – 6 drops of ethanol had to be added to continue stirring. TLCs were carried out at 30 min or 1 h intervals. Once the 2-naphthol spot no longer appeared on TLC or once its intensity did not appear to change, stirring was stopped and acetone (5 - 10 mL) was added to the mixture to dissolve all constituents. Stirring ensued for 30 more minutes before the catalyst was filtered using a sintered funnel. After concentrating the filtrate by rotary evaporation, the crude reaction mixture was loaded onto a silica-gel filled column solvated by a mixture of 9 : 1 *n*-hexane / ethyl acetate. The final product could be eluted after increasing the polarity of the solvent mixture by increasing the relative amount of ethyl acetate. After concentrating in the rotary evaporator and drying under vacuum created by an oil pump, a white/yellow solid was obtained. This was dissolved and recrystallized from boiling-hot ethanol before recording the yield. IR, NMR and MS analysis were ultimately performed to characterise the final product.

In order to test the recyclability of the catalyst, the same procedure above was repeated with the difference being that the catalyst was left to dry overnight in an oven set at 130 ^{0}C before reusing it in the subsequent trial run.

Analytical information for selected compounds

(6a) 1-(phenyl(pyrrolidin-1-yl)methyl)naphthalen-2-ol.[30] White crystals. M.P.: 166 ^{0}C. IR (NaCl): 3062, 3018, 2974, 2877, 2827, 1622, 1600, 1585, 1519, 1506, 1467, 1452, 1415, 1381, 1350, 1313, 1265, 1238, 1215, 1157, 1141, 1124, 1107, 1080, 1028, 950, 837, 815, 767, 630 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.85 (br s, 1H), 7.87 (d, *J* = 8.54 Hz, 1H), 7.69 (d, *J* = 8.13 Hz, 1H), 7.66 (d, *J* = 8.85 Hz, 1H), 7.60 (d, *J* = 8.19 Hz, 2H), 7.36 (ddd, *J* = 1.37, 6.87, 8.54 Hz, 1H), 7.26 - 7.29 (m, 1H), 7.22 - 7.25 (m, 1H), 7.18 - 7.22 (m, 2H), 7.15 (d, *J* = 8.85 Hz, 1H), 5.13 (s, 1H), 3.10 – 3.50 (br s, 1H), 2.00 – 2.75 (br s, 3H), 1.86 (br s, 4H).

(6b) 1-(4-methylphenyl(pyrrolidine-1-yl)methyl)naphthalen-2-ol.[31] Yellow crystals. M.P.: 120 ^{0}C. IR (NaCl): 3049, 3014, 2974, 2924, 2877, 2823, 1622, 1600, 1581, 1514, 1467, 1452, 1413, 1381, 1350, 1311, 1267, 1236, 1215, 1157, 1126, 1112, 952, 817, 756, 667, 628 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.89 (br s, 1H), 7.86 (d, *J* = 8.54 Hz, 1H), 7.68 (d, *J* = 7.32 Hz, 1H), 7.65 (d, *J* = 8.85 Hz, 1H), 7.48 (d, *J* = 8.19 Hz, 2H), 7.35 (ddd, *J* = 1.37, 6.94, 8.47 Hz, 1H), 7.18 - 7.23 (m, 1H), 7.14 (d, *J* = 8.85 Hz, 1H), 7.06 (d, *J* = 8.19 Hz, 2H), 5.10 (s, 1H), 3.09 – 3.47 (br s, 1H), 2.81 – 2.41 (br s, 2H) 2.30 - 2.40 (m, 1H), 2.25 (s, 3H), 1.85 (br s, 4H).

(6d) 1-(3-methoxyphenyl(pyrrolidine-1-yl)methyl)naphthalen-2-ol. Yellow crystals. M.P.: 110 ^{0}C. IR (NaCl): 3049, 305, 2970, 2875, 2833, 1622, 1600, 1585, 1521, 1489, 1452, 1436, 1413, 1381, 1350, 1303, 1269, 1238, 1157, 1124, 1049, 952, 894, 819, 752, 702, 667, 640 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.80 (br s, 1 H), 7.88 (d, *J*=8.70 Hz, 1 H), 7.69 (d, *J*=8.04 Hz, 1 H), 7.65 (d, *J*=8.85 Hz, 1 H), 7.37 (t, *J*=7.74 Hz, 1 H), 7.13 - 7.23 (m, 5 H), 6.73 (d, *J*=7.68 Hz, 1 H), 5.09 (s, 1 H), 3.74 (s, 3 H), 3.27 (br s, 1 H), 2.68 (br s, 1 H), 2.35 (br s, 1 H), 2.25 (br s, 1 H), 1.85 (br s, 4 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.71, 155.58, 142.80, 131.89, 129.60, 128.82, 128.57, 126.34, 122.32, 121.14, 120.88, 119.92, 116.50, 114.35, 112.80, 70.74, 55.14, 54.54, 52.41, 23.39. MS (ES+): m/z = 334.25 $[M+H]^{+}$, 304.20, 257.33, 219.19, 145.06, 55.18, 54.87.

(6e) 1-(4-methoxyphenyl(pyrrolidine-1-yl)methyl)naphthalen-2-ol.[32] Yellow crystals. M.P.: 92 ^{0}C. IR (NaCl): 3062, 3005, 2970, 2875, 2835, 1622, 1618, 1581, 1512, 1467, 1456, 1413, 1381, 1350, 1311, 1267, 1238, 1178, 1110, 1031, 952, 887, 829, 815, 748, 667, 628 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ 13.90 (br s, 1H), 7.84 (d, *J* = 8.54 Hz, 1H), 7.69 (d, *J* = 7.98 Hz, 1H), 7.65 (d, *J* = 8.85 Hz, 1H), 7.50 (d, *J* = 8.85 Hz, 2H), 7.36 (ddd, *J* = 1.37, 6.94, 8.54 Hz, 1H), 7.21 (ddd, *J* = 1.07, 6.87, 7.93 Hz, 1H), 7.14 (d, *J* = 8.85 Hz, 1H), 6.78 (d, *J* = 8.85 Hz, 2H), 5.09 (s, 1H), 3.72 (s, 3H), 3.10 - 3.44 (br s, 1H), 2.49 - 2.81 (m, 1H), 2.11 - 2.43 (m, 2H), 1.72 - 1.99 (br s, 4H).

(6j) 1-(4-pyridinyl(pyrrolidine-1-yl)methyl)naphthalen-2-ol. White crystals. M.P.: 150 ^{0}C. IR (NaCl): 3055, 3022, 2972, 2877, 2833, 1622, 1597, 1521, 1506, 1465, 1413, 1344, 1315, 1267, 1238, 1157, 1120, 950, 891, 817, 748, 667, 632, 617 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.37 (br s, 1H), 8.51 (d, *J* = 6.10 Hz, 2H), 7.84 (d, *J* = 8.54 Hz, 1H), 7.72 (d, *J* = 8.24 Hz, 1H), 7.69 (d, *J* = 8.85 Hz, 1H), 7.54 (d, *J* = 6.10 Hz, 2H), 7.41 (ddd, *J* = 1.37, 6.94, 8.47 Hz, 1H), 7.24 - 7.26 (m, 1H), 7.15 (d, *J* = 8.85 Hz, 1H), 5.12 (s, 1H), 2.60 (br s, 1H), 2.31 - 2.55 (m, 3H), 1.77 - 1.97 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.60, 150.36, 149.64, 131.59, 130.09, 129.07, 128.64, 126.69, 123.16, 122.67, 120.59, 119.90, 115.29, 69.65, 53.46 23.43. MS (ES+): m/z = 305.21 $[M+H]^{+}$,188.26, 162.07, 64.73, 51.01.

(6k) 1-(4-fluorophenyl(pyrrolidine-1-yl)methyl)naphthalen-2-ol.[33] Yellow crystals. M.P.: 146 ^{0}C. IR (NaCl): 3064, 3010, 2970, 2875, 2833, 1620, 1600, 1508, 1467, 1456, 1415, 1350, 1307, 1267, 1234, 1159, 1124, 1097, 952, 835, 817, 771, 744, 667, 626 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ 13.75 (br s, 1H), 7.82 (d, *J* = 8.54 Hz, 1H), 7.71 (d, *J* = 8.01 Hz, 1H), 7.67 (d, *J* = 8.85 Hz, 1H), 7.55 - 7.60 (m, 2H), 7.37 (ddd, *J* = 1.37, 6.87, 8.54 Hz, 1H), 7.23 (ddd, *J* = 0.92, 6.94, 8.01 Hz, 1H), 7.15 (d, *J* = 8.85 Hz, 1H),

6.92 - 6.98 (m, 2H), 5.12 (s, 1H), 3.01 – 3.52 (br s, 1H), 2.45 – 2.83 (br s, 1H), 2.05 – 2.46 (br s, 1H), 1.87 (br s, 4H).

(6n) 1-(3,4-dichlorophenyl(pyrrolidine-1-yl)methyl)naphthalen-2-ol. Yellow crystals. M.P.: 64 ^{0}C. IR (NaCl): 3061, 3014, 2972, 2877, 2833, 1622, 1600, 1519, 1469, 1454, 1413, 1350, 1319, 1269, 1236, 1215, 1157, 1122, 1031, 950, 896, 817, 748, 667, 636 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ 13.50 (br s, 1H), 7.78 (d, *J* = 8.54 Hz, 1H), 7.72 (d, *J* = 7.93 Hz, 1H), 7.67 - 7.70 (m, 2H), 7.47 (dd, *J* = 1.98, 8.39 Hz, 1H), 7.40 (ddd, *J* = 1.22, 7.02, 8.54 Hz, 1H), 7.33 (d, *J* = 8.24 Hz, 1H), 7.23 - 7.25 (m, 1H), 7.15 (d, *J* = 8.85 Hz, 1H), 5.08 (s, 1H), 3.02 – 3.49 (br s, 1H), 2.09 – 2.80 (br s, 3H), 1.79 - 2.01 (br s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.48, 132.63, 131.93, 131.55, 130.73, 130.28, 129.95, 129.03, 128.63, 127.79, 126.66, 122.63, 120.61, 119.98, 115.62, 69.60, 54.46, 52.43, 23.38. MS (ES+): m/z = 374.16 $[M+2]^+$, 372.07 $[M]^+$, 328.24, 304.07, 264.03, 229.25, 216.91, 214.95, 144.93, 90.92, 54.87.

(6r) 1-(4-methylphenyl(piperidine-1-yl)methyl)naphthalen-2-ol.[34] White crystals. M.P.: 145 ^{0}C. IR (NaCl): 3049, 3008, 2937, 2856, 2814, 1622, 1601, 1519, 1454, 1417, 1361, 1315, 1269, 1236, 1217, 1157, 1107, 1087, 1037, 945, 875, 839, 819, 756, 667, 611 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.00 (br s, 1H), 7.82 (d, *J* = 8.54 Hz, 1H), 7.67 (d, *J* = 7.70 Hz, 1H), 7.64 (d, *J* = 8.85 Hz, 1H), 7.42 (br s., 2H), 7.34 (ddd, *J* = 1.22, 6.94, 8.62 Hz, 1H), 7.19 (ddd, *J* = 1.22, 6.94, 8.01 Hz, 1H), 7.13 (d, *J* = 8.85 Hz, 1H), 7.05 (d, *J* = 8.24 Hz, 2H), 5.04 (s, 1H), 3.30 (br s, 1H), 2.67 (br s, 1H), 2.24 (s, 3H), 2.11 (br s, 1H), 1.91 (br s, 1H), 1.68 (br s, 4H), 1.56 (br s, 2H).

(6u) 1-((morpholino(4-methylphenyl)methyl)naphthalen-2-ol. White crystals. M.P.: 54 ^{0}C. IR (NaCl): 3055, 3012, 2963, 2920, 2853, 1622, 1506, 1456, 1414, 1362, 1314, 1271, 1234, 1119, 1072, 1003, 949, 878, 814, 768, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.14 (br s, 1H), 7.83 (d, *J* = 8.54 Hz, 1H), 7.69 (d, *J* = 7.93 Hz, 1H), 7.66 (d, *J* = 8.85 Hz, 1H), 7.44 (d, *J* = 8.24 Hz, 2H), 7.37 (ddd, *J* = 1.53, 7.02, 8.54 Hz, 1H), 7.23 (ddd, *J* = 1.07, 6.87, 7.93 Hz, 1H), 7.13 (d, *J* = 8.85 Hz, 1H), 7.08 (d, *J* = 8.24 Hz, 2H), 5.09 (s, 1H), 3.81 (br s, 4H), 3.11 (br s, 1H), 2.35 - 2.62 (m, 3H), 2.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.71, 137.99, 135.61, 132.35, 129.72, 129.66, 129.59, 128.90, 126.53, 122.58, 121.05, 119.76, 115.27, 71.72, 66.93, 53.96, 51.52, 21.05. MS (ES+): m/z = 334.25 $[M+H]^+$, 320.27, 278.20, 277.19, 259.23, 247.15, 233.17, 201.16, 161.82, 142.97, 105.02.

(6w) 1-((morpholino(4-cyanophenyl)methyl)naphthalen-2-ol. White crystals. M.P.: 94 ^{0}C. IR (NaCl): 3019, 2965, 2857, 2228, 1622, 1520, 1472, 1456, 1417, 1361, 1314, 1267, 1234, 1117, 949, 880, 818, 752, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.80 (s, 1H), 7.77 (d, *J* = 8.54 Hz, 1H), 7.68 – 7.75 (m, 4H), 7.58 (d, *J* = 8.54 Hz, 2H), 7.41 (ddd, *J* = 1.37, 6.94, 8.47 Hz, 1H), 7.25 – 7.30 (m, 1H), 7.14 (d, *J* = 8.85 Hz, 1H), 5.18 (s, 1H), 3.82 (br s, 4H), 2.15 – 2.65 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.74, 154.48, 144.11, 140.59, 138.80, 132.71, 132.01, 130.44, 129.16, 128.89, 126.94, 122.97, 120.44, 119.84, 118.29, 113.97, 112.20, 71.38, 66.71, 53.61, 51.91. MS (ES+): m/z = 345.25 $[M+H]^+$, 344.24 $[M]^+$, 343.23 $[M-1]^+$, 195.09, 172.95, 172.00.

(6x) 1-((butylamino)(phenyl)methyl)naphthalen-2-ol.[35] White crystals.M.P.: 146 ^{0}C. IR (NaCl): 3300, 3061, 3028, 2959, 2926, 2856, 1622, 1600, 1519, 1471, 1456, 1418, 1373, 1319, 1269, 1238, 1159, 1141, 1092, 939, 815, 765, 748, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.76 (m, 3H), 7.43 - 7.48 (m, 2H), 7.27 - 7.36 (m, 3H), 7.20 - 7.25 (m, 2H), 7.15 (d, *J* = 8.85 Hz, 1H), 5.67 (s, 1H), 2.83 (t, *J* = 7.17 Hz, 2H), 1.50 - 1.67 (m, 4H), 1.37 (sxt, *J* = 7.32 Hz, 2H), 0.91 (t, *J* = 7.48 Hz, 3H).

(6y) 1-((cyclopentylamino)(phenyl)methyl)naphthalen-2-ol. White crystals. M.P.: 128 ^{0}C. IR (NaCl): 3300, 3061, 3022, 2954, 2866, 1622, 1601, 1585, 1558, 1520, 1468, 1456, 1414, 1379, 1315, 1269, 1236, 1155, 1097, 943, 816, 744, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (br s, 1H), 7.69 - 7.74 (m, 3H), 7.40 - 7.45 (m, 2H), 7.27 - 7.36 (m, 3H), 7.20 - 7.25 (m, 2H), 7.15 (d, *J* = 8.85 Hz, 1H), 5.76 (s, 1H), 3.31 (br s, 1H), 2.02 - 2.10 (m, 1H), 1.89 - 1.97 (m, 1H), 1.62 - 1.75 (m, 2H), 1.55 - 1.61 (m, 2H), 1.39 - 1.53 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ157.32, 141.97, 132.56, 129.60, 129.15, 128.85, 127.99, 127.74, 126.44, 122.32, 121.12, 120.29, 113.63, 62.51, 58.92, 32.79, 32.34, 23.54, 23.58. MS (ES+): m/z = 319.32 $[M+2]^+$, 318.31 $[M+H]^+$, 304.01, 273.14, 233.04, 145.00, 86.17, 54.99.

(6z) 1-((isopentylamino)(phenyl)methyl)naphthalen-2-ol. White crystals. M.P.:122 ^{0}C. IR (NaCl): 3313, 3061, 3024, 2955, 2924, 2866, 1622, 1601, 1558, 1520, 1468, 1456, 1414, 1317, 1269, 1238, 1092, 941, 813, 745, 698 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.78 (m, 3H), 7.43 - 7.47 (m, 2H), 7.27 - 7.36 (m, 3H), 7.20 - 7.25 (m, 2H), 7.15 (d, *J* = 8.85 Hz, 1H), 5.67 (s, 1H), 2.84 (dd, *J* = 6.56, 8.09 Hz, 2H), 1.63 (td, *J* = 6.60, 13.35 Hz, 1H), 1.52 - 1.60 (m, 3H), 1.41 - 1.51 (m, 1H), 0.89 (d, *J* = 6.41 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.92, 141.74, 132.63, 129.64, 129.10, 128.84, 128.48, 128.07, 127.74, 126.41, 122.36, 121.16, 120.17, 113.41, 64.55, 47.48, 38.62, 26.07, 22.57, 22.51.MS (ES+): m/z = 320.27 $[M+H]^+$, 273.27, 249.04, 233.04, 176.18, 144.93, 88.07.

(6aa) 1-((benzylamino)(phenyl)methyl)naphthalen-2-ol.[36] White crystals. M.P.: 132 ^{0}C. IR (NaCl): 3310, 3061, 3028, 2853, 1620, 1600, 1583, 1520, 1494, 1467, 1452, 1414, 1317, 1269, 1238, 1157, 1072, 1028, 939, 818, 742, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.55 (br s, 1H), 7.72 - 7.77 (m, 2H), 7.69 (d, *J* = 8.54 Hz, 1H), 7.26 - 7.40 (m, 9H), 7.19 - 7.26 (m, 4H), 5.76 (s, 1H), 4.06 (d, *J* = 13.12 Hz, 1H), 3.83 (d, *J* = 13.12 Hz, 1H).

(6bb) 1-((benzylamino)(4-cyanophenyl)methyl)naphthalen-2-ol. White crystals. M.P.: 54 ^{0}C. IR (NaCl): 3302, 3061, 3028, 2853, 2228, 1622, 1601, 1558, 1520, 1468, 1454, 1414, 1269, 1238, 1159, 1076, 1018, 939, 820, 748, 698 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ 13.12 (br s, 1H), 7.75 - 7.79 (m, 2H), 7.61 (d, *J* = 8.54 Hz, 1H), 7.56 (d, *J* = 8.54 Hz, 2H), 7.51 (d, *J* = 8.54 Hz, 2H), 7.32 - 7.40 (m, 4H), 7.26 - 7.31 (m, 3H), 7.20 (d, *J* = 8.85 Hz, 1H), 5.80 (s, 1H), 4.03 - 4.10 (m, 1H), 3.82 (d, *J* = 12.82 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$,) δ 156.74, 146.23, 137.47, 132.89, 132.39, 130.47, 129.12, 128.94, 128.64, 128.56, 128.05, 126.88, 122.84, 120.60, 120.15, 118.40, 112.01, 111.92, 61.82, 52.59. MS (ES+): m/z = 365.11 $[M+H]^+$, 221.02, 196.04, 186.99, 144.68, 143.98, 107.93, 90.92, 88.89.

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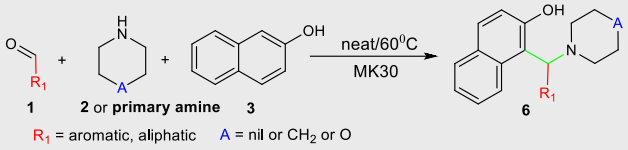

The one-pot multicomponent Betti synthesis was performed under green heterogeneous and neat conditions in the presence of Montmorillonite K30 catalyst, which is safe, cheap, and commercially available and does not require any preparations. It is fully recoverable and recyclable for up to 5 runs. Both secondary and primary aliphatic amines give products in good to excellent yields. The developed protocol displays a very high Atom Economy and a low E-Factor.

Multi-component reactions • Green chemistry • One-pot • Heterogeneous catalysis

Giovanna Bosica, Roderick Abdilla and Kaylie Demanuele*

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Revisiting the Betti synthesis: using a cheap, readily-available, recyclable clay catalyst in solventless conditions