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Calix[*n*]arenes: active organocatalysts for the synthesis of densely functionalized piperidines by one-pot multicomponent procedure

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ABSTRACT

An efficient, suitable and high yielding method has been developed for the synthesis of different densely functionalized piperidine derivatives via pseudo-five component, one-pot domino reaction through a combination of β-ketoesters, aromatic aldehydes, and various amines using *p*-sulfonic acid calix[*n*]arenes as catalysts. The reaction was carried out in refluxing methanol, affording very good yields of the expected piperidine. Atomic economy, environmentally benign procedure, reuse of catalysts, and short reaction time are some of the important features of this protocol.

Introduction

Calix[*n*]arenes are macrocyclic compounds of phenolic units linked by methylene groups at the 2,6-positions, with defined upper and lower rims and a central annulus (Fig. 1). Calix[*n*]arenes, together with cyclodextrins, cucurbiturils, porphyrins, and crown ethers, constitute the most important classes of macrocyclic organic host compounds.[1]

There are a large number of applications involving calix[*n*]arenes, due to their easy structural modification.[1] In the last two decades, numerous applications of calix[*n*]arenes in supramolecular chemistry have been reported in the literature.[2]

Among all calix[*n*]arenes known so far, *p*-sulfonic acid calix[*n*]arenes have been shown to be the most efficient catalysts for Biginelli,[3] Hantzsch,[4] Povarov[5] Mannich-type[6] and esterification[7] reactions and in the synthesis of 2-arylpiridines,[4] xanthenones,[8] and dihydro-β-carboline derivatives.[9] Although the use of calix[*n*]arenes as catalysts in various reactions has been reported, there is, to the best of our knowledge, no report in the literature on the use of these compounds as catalysts in the synthesis of densely functionalized piperidines via pseudo-five component reactions.

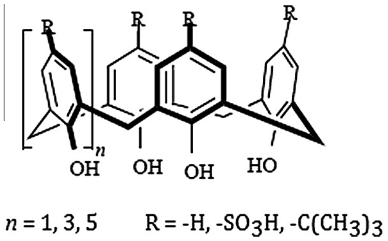

Figure 1. Calix[*n*]arene basic structure.

In the context of Green Chemistry, the design and development of sequences allowing a highly selective access to elaborated molecular scaffolds, combining structural diversity with eco-compatibility, are great challenges for organic chemists[10]. In this context, multicomponent reactions (MCRs) have emerged as an important alternative, because three or more reactions are combined in one synthetic step to obtain a unique product without formation of by-products. In most cases, the atomic economy is very high. Also, the environmental compatibility of these processes can also be considerably improved if an appropriate catalyst is used.

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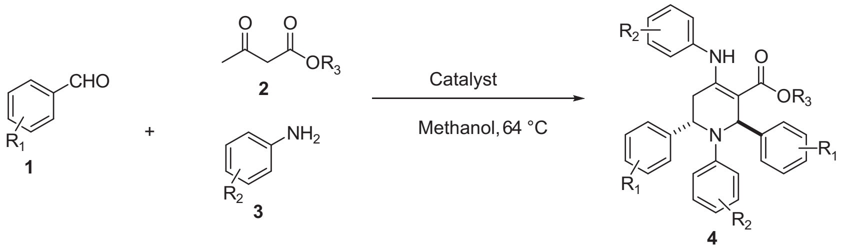


Scheme 1. Synthesis of functionalized piperidines.

Other advantages are related to the selectivity, mild reaction conditions, and the fact that the catalysts are recoverable and recyclable from the reaction medium.[11]

On the other hand, piperidines and their analogues are important heterocycles that are present in many naturally occurring alkaloids, biologically active compounds, and organic fine chemistry. Some of them act as pharmaceutical agents.[12] Compounds containing piperidine as sub structure exhibit anti-bacterial,[13] anti-malarial,[14] anti-inflammatory,[15] and anti-hypertensive activity,[16] are α_1-AB antagonists,[17] and acts as therapeutic agents in the treatment of influenza infection activities,[18] and cancer metastasis,[19] among others.

Thus, the synthesis of highly substituted piperidines has gained considerable attention and as a result a number of methodologies have been developed using several approaches involving a variety of cyclization techniques.[20] In general these methods suffer from the drawbacks of multistep synthesis and a lower yield in the overall process of the desired product.[21]

In 2007, Clarke and coworkers report a five-component condensation reaction for the formation of highly substituted piperidines. The procedure involves the simultaneous reaction between methyl or ethyl acetoacetate, two equivalents of aldehyde and amines in the presence of $InCl_3$ in acetonitrile at 20 °C.[22] The high-atom economy, good yields, mild reaction condition, simple experimental setup, eco-friendliness and stereo specificity of this methodology, have prompted the development of new protocols using different recyclable catalysts. Recently, the synthesis of highly functionalized piperidines has been reported using the multicomponent reaction in the presence of acetic acid,[23] $Ce(OTf)_4$,[24] $H_3[PW_{12}O_{40}]$,[25] $[K^+PEG]Br_3$,[21] $Bi(NO_3)_3{\cdot}5H_2O$,[20] BF_3-SiO_2,[26] *p*-TSA,[27] Zn^{+2} hydrogen sulfate,[28] $InCl_3$,[22] amount others.

As part of the ongoing efforts to achieve new catalysts for the synthesis of heterocyclic compounds, we report a one-pot multicomponent synthesis of highly functionalized piperidine derivatives by condensing β-keto esters, aryl aldehydes, and arylamines in the presence of catalytic amounts of *p*-sulfonic acid calix[*n*]arenes as recyclable organocatalyst (Scheme 1).

Results and discussion

Herein we describe an efficient and simple method for the synthesis of densely functionalized piperidines by one-pot multicomponent synthesis using calix[*n*]arenes as organocatalysts. The *p*-sulfonic acid calix[4]arene and *p*-sulfonic acid calix[6]arene used as catalysts were synthesized in our laboratory following the literature procedures. *p-tert*-Butyl-calix[*n*]arenes were prepared by the Gutsche and Iqbal method,[29] followed by a dealkylation by treatment with aluminum chloride in the presence of toluene and phenol according to Ungaro and coworkers,[30] finally the addition of concentrated sulfuric acid (98 wt%) afforded the *p*-sulfonic acid calix[4]arene and *p*-sulfonic acid calix[6]arene (Shinkai et al.) (purity > 99%, elemental analysis).[31]

Table 1
Screening of calix[*n*]arenes as organocatalysts for synthesis of functionalized piperidines[a]

Entry	Catalyst	Yield (%)
1	–	–
2	*n* = 1, R = t-Bu (**a**)	54
3	*n* = 1, R = SO_3H (**b**)	73
4	*n* = 3, R = t-Bu (**c**)	50
5	*n* = 3, R = SO_3H (**d**)	70
6	PTSA	63

[a] Reaction conditions: see Note 35.

In the first experiment, the one-pot three-component reaction between benzaldehyde, aniline, and methyl acetoacetate was chosen as the model reaction to optimization of catalyst type, solvent, amount of catalyst, and temperature. Preliminary studies focused on the screening of calix[*n*]arenes (**a**–**d**) through the piperidine synthesis containing benzaldehyde, aniline, and methyl acetoacetate. Initially we performed a blank experiment in ethanol as solvent, and no product was obtained in the absence of the catalyst (Table 1, entry 1) indicating that the catalyst is necessary for the reaction.

The use of *p-tert*-butyl-calix[*n*]arenes **a** or **c** (Table 1, entries 2 and 4) has raised the yields to 54% and 50%, respectively, and the substitution of *p-tert*-butyl for a *p*-sulfonyl group (calix[*n*]arenes **b** and **d**) allowed obtaining piperidines in yields higher than 73% and 70%, respectively (Table 1, entries 3 and 5). The improvement of reaction yield from the use of *p*-sulfonic acid calix[*n*]arenes is likely due to their increased acidity.[3] Overall, calix[*n*]arenes **b** and **d**, were slightly more efficient and selective than PTSA (*p*-toluensulfonic acid), 63% (Table 1, entry 6). In this case, several secondary products were detected by TLC.

Large scale reactions carried out with benzaldehyde, aniline, and methyl acetoacetate at 5, 10, and 15 mmol, respectively, provided similar reactions with good yields. The promising results obtained with *p*-sulfonic acid calix[4]arene **b** prompted us to further investigate the effect of solvents on piperidine synthesis reactions catalyzed by this macrocyclic compound.

Methanol (Table 2, entry 1) followed by ethanol and acetonitrile showed from good to acceptable performances as solvents, while hexane proved to be unsuitable. Finally, the reaction was carried out in solvent-free conditions with moderate yields (51%; entry 5), probably due to the lack of effective interaction of reactants with the catalyst as reported.[20] In this case several unidentified products were detected by TLC. The next experiments were performed using methanol as solvent reaction.

The effect on the amount of catalyst on the yield of piperidine was then checked (Table 3). The experimental reaction conditions were: benzaldehyde (1 mmol), aniline (1 mmol), methyl acetoacetate (0.5 mmol), and a variable amount of the catalyst (0.5, 1, 1.5, 2, and 4 mmol%). The yields increased up to 73% when the amount of catalyst was increased from 0.5 to 1.5 mmol%. No relevant changes were observed with further increase in the amount of

Table 2
Effect of solvent on the yields of *p*-sulfonic acid calix[4]arene—catalyzed pyperidine reaction[a]

Entry	Solvent	Yield (%)
1	Methanol	73
2	Ethanol	68
3	Acetonitrile	40
4	Hexane	—
5	Solvent-free	54

[a] Reaction conditions: except for solvent, see Note 35.

Table 3
Effect of the amount of catalyst *p*-sulfonic acid calix[4]arene on the yields piperidine reaction[a]

Entry	Catalyst (mmol%)	Yields (%)
1	0.5	35
2	1	55
3	1.5	73
4	2	73
5	4	74

[a] Reaction conditions: except for catalyst amount see Note 35.

catalyst (4 mmol%), 74%. Thus 1.5 mmol% of catalyst was a suitable amount in this reaction.

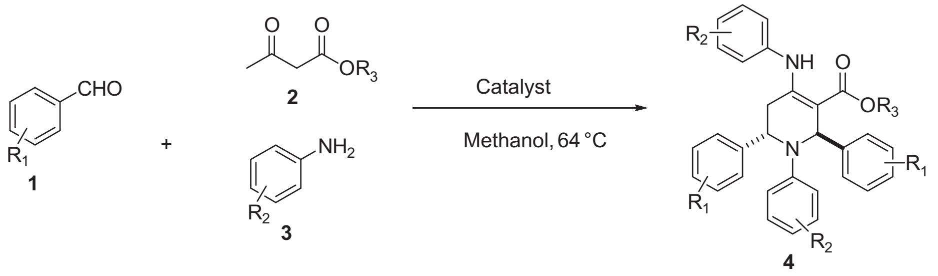
To explore the scope and generality of five-component reaction under optimized conditions, a variety of aromatic aldehydes containing electron donating or electron withdrawing substituents in the aromatic ring such as –H, 4-CH_3, 4-OCH_3, 4-SCH_3, 4-Cl, 4-NO_2 and 4-F, were reacted with β-keto esters (methyl and ethyl acetoacetate) and a number of substituted anilines such as –H, 4-CH_3, 4-Cl. The reaction yields for each product **4a**–**t** are shown in Table 4.

A mixture of benzaldehyde, aniline, and methyl acetoacetate reacted under the standard condition furnished the corresponding piperidine **4a** in 73% (Table 4, entry 1). A general trend was observed: aldehydes bearing electron-withdrawing functional groups react efficiently with methyl or ethyl acetoacetate in the presence of substituted anilines to generate the corresponding product in very good yields (Table 4). However in the cases of 4-nitrobenzaldehyde very poor yields (<5%) (not show in Table 4) was obtained. As suggested by G. Brahmachari et al.,[20] the *p*-nitro group allows the formation of a very stable imine, having an extra conjugation, which is less reactive in methanol. Similarly, aliphatic aldehyde as *n*-butanal and *n*-propanal, (not show in Table 4) did not give the desired reaction products. In addition, other hindered aldehydes (e.g., 3-formylcromone), also fail to give the expected product.

The present methodology, was also examined using two β-ketoester (methyl and ethyl acetoacetate) with varying aldehydes and anilines, where the desired products were obtained in very good yields (Table 4).

Finally, several anilines with substituent as –H, 4-Me, 4-Cl, 4-NO_2, 3-NO_2, and 2,6-diMe were treated with aldehydes and β-keto esters under similar conditions. Some examples provide the corresponding piperidine with very good yields with exception of nitro anilines and 2,6-dimethylaniline which give yields below 5%, (not showed in Table 4) presumable due to electronic and steric

Table 4
p-Sulfonic acid calix[4]arene—catalyzed synthesis of functionalized pyridine scaffolds[a]



R^1	R^2	R^3	4 (*syn:anti*) ratio	Yield (%)	Mp (°C) Found	Mp (°C) reported
H	H	Me	**a** (0:100)	73	192–195	193–195[24]
H	4-Cl	Me	**b** (0:100)	68	201–203	202–203[20]
H	4-Me	Me	**c** (0:100)	72	221–224	220–222[20]
4-Me	H	Me	**d** (0:100)	73	212–213	213–215[32]
4-Cl	H	Me	**e** (0:100)	68	188–190	189–191[32]
4-F	H	Me	**f** (0:100)	67	160–162	160[14]
4-OMe	H	Me	**g** (10:90)	72	178–180	180[14]
4-OMe	4-Cl	Me	**h** (8:92)	70	192–195	195[14]
4-Cl	4-Cl	Me	**i** (0:100)	66	190–192	—[b]
4-F	4-Cl	Me	**j** (0:100)	67	174–177	175–177[20]
4-OMe	4-Me	Me	**k** (9:91)	70	180–182	181[32]
4-Me	4-Me	Me	**l** (0:100)	71	210–212	211–213[20]
H	H	Et	**m** (17:83)	61	172–175	173–174[24]
H	4-Cl	Et	**n** (0:100)	59	198–200	199–201[24]
4-OMe	H	Et	**o** (0:100)	62	158–160	No data[33]
4-SMe	H	Et	**p** (0:100)	68	170–173	—[b]
4-OMe	4-Cl	Et	**q** (10:90)	68	210–213	—[b]
4-Me	4-Me	Et	**r** (0:100)	67	219–221	—[b]
4-SMe	4-Cl	Et	**s** (7:93)	68	187–190	—[b]
H	4-Me	Et	**t** (0:100)	60	197–200	198–200[24]

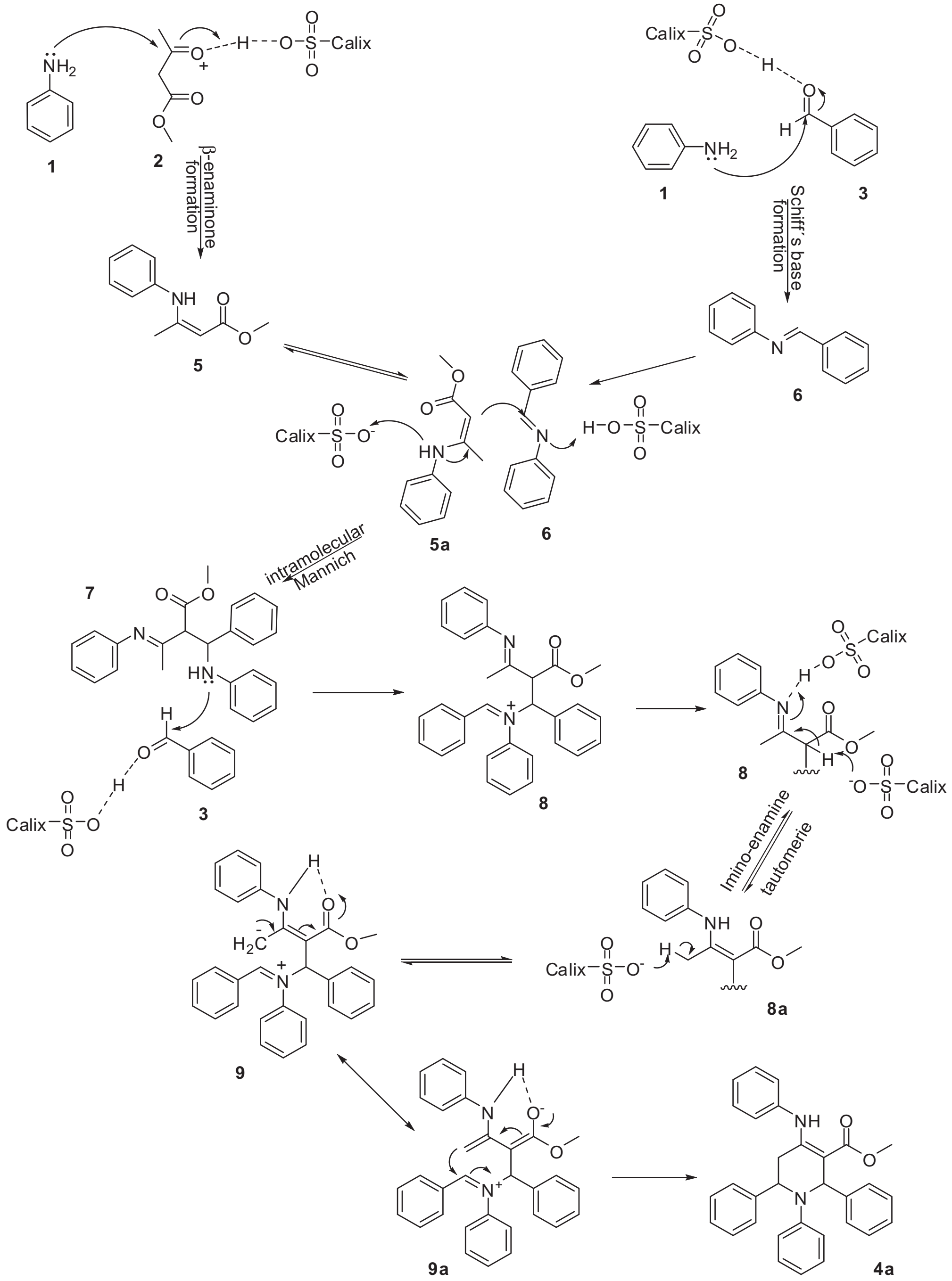
[a] Reaction conditions: see Note 35.
[b] New compound.

effects. Similarly aliphatic amines as *n*-butylamine fail to give the corresponding piperidine due to its higher basicity compared with anilines.

A plausible mechanism for the formation of these functionalized piperidines is outlined in Scheme 2. A similar mechanism was postulated by Balijapalli et al.[23] In the first step, the aniline reacts with the activated alkyl acetoacetate to give the β-enaminone (**5**) which was detected by TLC. After the addition of benzaldehyde, the reaction with aniline forms the corresponding Schiff's base **6**. Further, the enamine **5** and Schiff's base **6** underwent intermolecular Mannich reaction in the presence of the catalyst to afford the imino intermediate **7**. A second activated benzaldehyde reacts with intermediate **7** to generate the intermediate **8** (second Schiff's base formation). The intermediate **8** underwent catalyzed imine-enamine tautomerization to form **8a**. The action of a base forms a more intermediate carbanion **9** stabilized by resonance (**9b**). The last structure underwent intramolecular cyclization to give functionalized piperidine derivatives **4a**.

All the products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. All data are well matched with the literature-reported compounds.[14,24,32,33] The relative stereochemistry of this class of compounds has been confirmed by single X-ray crystallographic analysis,[27] and the stereochemistry of our products was proved by comparison of spectroscopy data of some products with those of eutectics samples (see Note 34, 36 and 37).

Finally, in order to quantify how much 'greener' the methodology is, the Atomic Economy (AE), Atomic efficiency factor (E), Process Mass Intensity (PMI) and Reaction mass efficiency (RME) were



Scheme 2. Possible mechanism for the formation of piperidines 4.

Table 5
Green metric parameter for the reaction between benzaldehyde, aniline and methyl acetoacetate

Entry	Parameters	Green metrics values[a]
1	E-factor (including mass of solvent and catalyst	28.77
2	E-factor (excluding mass of solvent and catalyst	0.53
3	Atomic economy	89.5%
4	Process mass intensity (PMI)	29.77
5	Process mass intensity (PMI) (excluding mass of solvent and catalyst)	1.53
6	Reaction mass efficiency (RME)	0.65

[a] Full calculi of green metrics values are presented in Supplementary Material.

calculated for the model reaction between aniline, benzaldehyde, and methyl acetoacetate (Table 5).

Conclusions

A general methodology is reported for the preparation of highly functionalized piperidines in the presence of *p*-sulfonic acid calix[4]arene organocatalysts via one pot five components reaction from simple available starting materials. The relevant features of this methodology are good yields, mild reaction conditions, atom economy, friendly with the environment, and the cost effectiveness. The catalysts are used and recycled without appreciable reduction of the catalytic activity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.090.

References and notes

1. Simoes, J. B.; da Silva, D. L.; de Fatima, A.; Fernandes, S. A. *Curr. Org. Chem.* **2012**, *16*, 949.
2. Jose, P.; Menon, S. *Bioinorg. Chem. Appl.* **2007**, 2007.
3. da Silva, D. L.; Fernandes, S. A.; Sabino, A. A.; Fátima, Â. d. *Tetrahedron Lett.* **2011**, *52*, 6328.
4. Sathicq, Á. G.; Liberto, N. A.; Fernándes, S. A.; Romanelli, G. P. C. R. *Chimia* **2015**, *18*, 374.
5. Simoes, J. B.; de Fatima, A.; Sabino, A. A.; de Aquino, F. J. T.; da Silva, D. L.; Barbosa, L. C. A.; Fernandes, S. A. *Org. Biomol. Chem.* **2013**, *11*, 5069.
6. Shimizu, S.; Shimada, N.; Sasaki, Y. *Green Chem.* **2006**, *8*, 608.
7. Fernandes, S. A.; Natalino, R.; Gazolla, P. A. R.; da Silva, M. J.; Jham, G. N. *Tetrahedron Lett.* **2012**, *53*, 1630.
8. da Silva, D. L.; Silva Terra, B.; Ribeiro Lage, M.; Lucia Tasca GoisRuiz, A.; Capeletti da Silva, C.; Ernesto de Carvalho, J.; Walkimarde Mesquita Carneiro, J.; Terra Martins, F.; Antonio Fernades, S.; de Fatima, A. *Org. Biomol. Chem.* **2015**, *13*, 3280.
9. Santos, L. S.; Fernandes, S. A.; Pilli, R. A.; Marsaioli, A. J. *Tetrahedron Asymmetry* **2003**, *14*, 2515.
10. Isambert, N.; Duque, M. d. M. S.; Plaquevent, J.-C.; Genisson, Y.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347.
11. Sheldon, R. A.; Arends, I. W. C. E.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH, 2007.
12. Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett.* **2010**, *51*, 4419.
13. Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1206.
14. Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009**, *17*, 625.
15. Ho, B.; Michael Crider, A.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 265.
16. Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. *Eur. J. Med. Chem.* **1991**, *26*, 19.
17. Li, J. B.; Xia, L.; Wu, B.; Wang, T.; Jiang, Z. Z. *Chin. Chem. Lett.* **2008**, *19*, 1193.
18. Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Babu, Y. S.; Bantia, S.; Elliott, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379.
19. Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935.
20. Brahmachari, G.; Das, S. *Tetrahedron Lett.* **2012**, *53*, 1479.
21. Verma, S.; Jain, S. L.; Sain, B. *Beilstein J. Org. Chem.* **2011**, *7*, 1334.
22. Clarke, P. A.; Zaytzev, A. V.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, *48*, 5209.
23. Balijapalli, U.; Munusamy, S.; Sundaramoorthy, K. N.; Iyer, S. K. *Synth. Commun.* **2014**, *44*, 943.
24. Khaksar, S.; Vahdat, S. M.; Alipour, M. *C. R. Chim.* **2013**, *16*, 1024.
25. Khaksar, S.; Meysam Baghbanian, S.; Barsan, N. *Comb. Chem. High Throughput Screening* **2014**, *17*, 503.
26. Ramachandran, R.; Jayanthi, S.; Jeong, Y. T. *Tetrahedron* **2012**, *68*, 363.
27. Sajadikhah, S. S.; Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Shams-Najafi, S. J. *Monatsh. Chem.* **2012**, *143*, 939.
28. Majid, G. *Lett. Org. Chem.* **2012**, *9*, 497.
29. Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234.
30. Casnati, A.; Ca, N. D.; Sansone, F.; Ugozzoli, F.; Ungaro, R. *Tetrahedron* **2004**, *60*, 7869.
31. Shinkai, S.; Araki, K.; Tsubaki, T.; Arimura, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2297.
32. Mishra, S.; Ghosh, R. *Tetrahedron Lett.* **2011**, *52*, 2857.
33. Kar, P.; Mishra, B. G.; Pradhan, S. R. J. *Mol. Catal. A-Chem.* **2014**, *387*, 103.

Further Reading

34. *General:* All reagents were commercial products used without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck silica gel GF 254 plates. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were measured on a Bioamerican melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 250 and/or 300 MHz. Chemical shifts (δ scale) are reported in parts per million (ppm) with TMS as internal reference. ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity, coupling constant (J value expressed in Hertz (Hz)) and number of protons. Signals were characterized as: s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad singlet).
35. *General procedure for the synthesis of highly functionalized piperidines:* To a solution of amine (1 mmol) and methyl or ethyl acetoacetate (0.5 mmol) in 5 mL of methanol was added 1.5 mmol% of catalyst and stirred at reflux temperature (64 °C). After 1 h, aromatic aldehyde (1 mmol) was added to the reaction mixture, and the stirring was continued after completion (TLC). The reaction mixture was concentrated and the precipitate was filtered off and washed with methanol (1 mL) to give the pure products.
36. *^{1}H and ^{13}C NMR chemical shifts of new compounds* ***4i*** *and* ***4p–s***
Compound ***4i****:* ^{1}H NMR (300 MHz; $CDCl_3$) δ = 2.69 (1H, dd, J = 2.5 and 15.1 Hz, H5a), 2.83 (1H, dd, J = 5.5 and 15.1 Hz, H5b), 3.94 (3H, s, O-CH_3), 5.07 (1H, br s, H6), 6.29 (1H, s, H2), 6.33 (2H, br d, J = 8.5 Hz, H_{orto} from Ar-NH), 6.37 (2H, br d, J = 9.0 Hz, H_{orto} from Ar-N), 6.98–7.32 (12H, m, Ar-H), 10.21 ppm (1H, s, NH). ^{13}C NMR (75 MHz; $CDCl_3$) δ = 168.2, 155.3, 145.0, 141.6, 140.4, 136.1, 133.3, 132.5, 131.8, 129.2, 129.0, 128.9, 128.6, 127.9, 127.7, 127.0, 121.9, 114.1, 98.1, 57.5, 54.9, 51.4, 33.6 ppm. Anal. Calcd for $C_{31}H_{24}Cl_4N_2O_2$: C, 70.32; H, 4.95; found: C, 70.33; H, 4.93.
Compound ***4p****:* ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (3H, t, J = 7.0 Hz, CH_3CH_2–), 2.48 (6H, br s, CH_3S–), 2.76 (1H, br d, $J \sim$ 15 Hz, H5a), 2.86 (1H, dd, J = 5.5 and 15.1 Hz, H5b), 4.26–4.39 (1H, m, CH_3CH_aH–), 4.40–4.54 (1H, m, CH_3CHH_b–), 5.09 (1H, br s, H6), 6.31–6.69 (7H, m, H2 + $H_{orto,\ para}$ from Ar-NH and Ar-N), 7.03–7.37 (12H, m, Ar-H), 10.30 ppm (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 156.0, 139.6, 137.8, 129.3, 128.9, 127.2, 126.9, 126.6, 125.7, 125.2, 116.3, 112.9, 98.0, 59.7, 57.6, 54.7, 33.6, 16.0, 15.9, 14.8 ppm. Anal. Calcd for $C_{34}H_{34}N_2O_2S_2$: C, 72.05; H, 6.05; found C, 72.02; H, 6.03.
Compound ***4q****:* ^{1}H NMR (300 MHz; $CDCl_3$) δ = 1.47 (3H, t, J = 7.1 Hz, CH_3CH_2–), 2.70 (1H, dd, J = 2.4 and 15.1 Hz, H5a), 2.85 (1H, dd, J = 5.5 and 15.1 Hz, H5b), 3.79 (3H, s, CH_3ArNH–)*, 3.81 (3H, s, CH_3ArN–)*, 4.25–4.40 (1H, m, CH_3CH_aH–), 4.41–4.54 (1H, m, CH_3CHH_b–), 5.06 (1H, br s, H6), 6.28 (2H, br d, J = 8.5 Hz, H_{orto} from Ar-NH), 6.31 (1H, s, H2), 6.45 (2H, br d, J = 9.2 Hz, H_{orto} from Ar-N), 6.80–7.23 (8H, m, Ar-H), 10.27 (0.9H, s, NH), 10.63 (0.1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.2, 158.9, 158.3, 155.5, 145.6, 136.6, 135.2, 134.1, 131.2, 129.0, 128.7, 127.6, 127.4, 126.9, 121.2, 114.2, 114.1, 113.7, 99.0, 59.9, 57.6, 55.3, 55.3, 54.8, 33.6, 14.8 ppm. Chemical shifts marked with * are interchangeables. Anal. Calcd for $C_{34}H_{32}Cl_2N_2O_4$: C, 67.66; H, 5.34; found: C, 67.67; H, 5.35.
Compound ***4r****:* ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (3H, t, J = 7.2 Hz, CH_3CH_2–), 2.17 (3H, s, CH_3ArNH–)*, 2.28 (3H, s, CH_3ArN–)*, 2.33 (3H, s, CH_3Ar-C2)$^{\#}$, 2.35 (3H, s, CH_3Ar-C6)$^{\#}$, 2.74 (1H, dd, J = 2.2 and 15.0 Hz, H5a), 2.84 (1H, dd, J = 5.0 and 15.0 Hz, H5b), 4.25–4.39 (1H, m, CH_3CH_aH–), 4.40–4.50 (1H, m, CH_3CHH_b–),

5.09 (1H, br s, H6), 6.20 (2H, br d, $J = 7.9$ Hz, H_{orto} from Ar-NH), 6.38 (1H, s, H2), 6.45 (2H, br d, $J = 8.3$ Hz, H_{orto} from Ar-N), 6.82–7.28 (12H, m, Ar-H), 10,22 (0.92H, s, NH), 10.57 ppm (0.08H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 168.3$, 156.4, 144.9, 141.4, 139.9, 136.4, 135.6, 135.3, 129.8, 129.3, 129.2, 128.8, 126.5, 126.3, 125.9, 124.8, 115.5, 112.8, 97.8, 59.5, 57.9, 55.0, 33.6, 21.1, 21.0, 20.8, 20.1, 14.8 ppm. Chemical shifts marked with * and $^\#$ are interchangeables. Anal. Calcd for $C_{36}H_{38}N_2O_2$: C, 81.47; H, 7.22; found: C, 81.42; H, 7.20.

Compound ***4s****:* ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.54$ (3H, brt, $J = 6.5$ Hz, CH_3CH_2–), 2.56 (3H, s, CH_3SAr-C2–)*, 2.57 (3H, s, CH_3SAr-C6–)*, 2.77 (1H, br d, $J \sim 15$ Hz, H5a), 2.92 (1H, dd, $J = 4.7$ and 14.5 Hz, H5b), 4.20–4.60 (2H, m, $CH_3CH_aH_b$–), 5.12 (1H, br s, H6), 6.36 (2H, br d, $J = 7.5$ Hz, H_{orto} from Ar-NH), 6.38 (1H, s, H2), 6.49 (2H, br d, $J = 8.0$ Hz, H_{orto} from Ar-N), 7.00–7.45 (12H, m, Ar-H), 10.01 (0.07H, s, NH), 10.33 ppm (0.93H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 168.0$, 155.3, 145.3, 140.2, 138.9, 137.6, 136.3, 131.4, 129.0, 128.7, 127.0, 126.9, 126.8, 126.6, 114.0, 98.5, 59.9, 57.7, 54.9, 33.5, 15.8, 14.7 ppm. Chemical shifts marked with * are interchangeables. Anal. Calcd for $C_{36}H_{38}N_2O_2S_2$: C, 72.69; H, 6.44; found: C, 72.63; H, 6.45

37. *Catalyst reuse:* was evaluated by the reaction of benzaldehyde, methyl acetoacetate and aniline in the presence of the catalyst using methanol of reaction solvent in identical experimental condition. After completion of the reaction, the mixture reaction was concentrated and the product was obtained by filtration. The liquid phase was completely evaporated and the residue was extracted with water (2 × 3 mL). After drying, the residue was used in successive reactions. The catalyst exhibited good catalytic activity up to four cycles (73%, 72%, 72%, and 70%).