


 Cite this: *RSC Adv.*, 2021, 11, 1271

β -Cyclodextrin: a supramolecular catalyst for metal-free approach towards the synthesis of 2-amino-4,6-diphenylnicotinonitriles and 2,3-dihydroquinazolin-4(1*H*)-one[†]

 Bijeta Mitra,^a Gyan Chandra Pariyar^b and Pranab Ghosh *^a

β -Cyclodextrin, a green and widespread supramolecular catalyst, has been explored as a highly proficient promoter for the metal-free one-pot multi-component synthesis of a vast range of highly functionalized bioactive heterocyclic moiety, 2-amino-4,6-diphenylnicotinonitriles and 2,3-dihydroquinazolin-4(1*H*)-one, from easily available precursor aldehydes. The main endeavor of these protocols is to explore this organic supramolecule in one-pot multi-component synthesis. Absence of metal catalyst or toxic acid and harsh reaction conditions, excellent functional group tolerance, inexpensive, greener and environmentally safe protocol are the key advantages of this work.

 Received 10th November 2020
 Accepted 8th December 2020

DOI: 10.1039/d0ra09562a

rsc.li/rsc-advances

1. Introduction

In organic transformations, a major apprehension focuses on catalysts and solvents. Pyrophoric property and the hazardous nature of solvent with high volatility and poor recovery are the major limitations of solvents. The main limitation of the metal catalyst is that it leads to metal contagion at the end of the reaction, which is not good for our Mother Earth. These disadvantages could be overcome using any green solvent and organocatalyst, which is good for the environment. We have developed a metal-free protocol using a supramolecular catalyst, β -cyclodextrin.¹ In terms of environmentally friendly and atom economy, water² as a reaction medium is highly advantageous.

Given the advancements in supramolecular chemistry and homogeneous catalysis, the supramolecular catalyst has been emerging as an important tool in synthesizing organic heterocyclic compounds.³ Among the array of supramolecular hosts, cyclodextrins (CDs) are one of the important enzyme models.^{4–7} Being cyclic oligosaccharides, cyclodextrins possess hydrophobic cavities, which enable them to bind with substrates selectively, because of which they are able to catalyze chemical reactions and ensure high selectivity.^{8–12} During the course of the reaction, CDs can reversibly bind to a host–guest complex with the substrates *via* non-covalent bonding, thus forming a complex, which is responsible for altering product distribution during organic reactions. The characteristics are attributed

to the development of geometrical constraints developed in the guest molecules because it gets included within the cavity of CDs. Similar to β -cyclodextrin, it uses the hydrophobic cavity to encapsulate biologically active molecules from aqueous solutions, which eventually enhances the bioavailability and stability of drug molecules. These properties have made CDs an important asset for pharmaceutical industries. Moreover, CDs are easily recyclable, easily available, cheaper, and non-toxic.^{13,14}

In the past few decades, for producing a diverse array of heterocyclic molecules and making the synthetic route simpler, one-pot multi-component organic synthesis has played an imperative role in chemistry. Three or sometimes more starting materials coalesce together in the same pot to exclusively develop the target molecule in multi-component synthesis without separating the intermediate, which aids in reducing the reaction time, solvent waste, and energy consumption and therefore have considerable compensation over the multistep procedure.¹⁵

The pyridine motif is an essential scaffold because of its occurrence in natural products, biological and medicinal products. Among pyridine ring systems, 2-aminonicotinonitrile derivatives have achieved elevated synthetic attention as an imperative heterocyclic molecule because of its existence as bio-active species such as IKK- β inhibitors,¹⁶ potent inhibitor of HIV-1 integrase,¹⁷ A2A adenosine receptor antagonist¹⁸ as well as in antitubercular,¹⁹ anticancer, anticonvulsant²⁰ and antimicrobial drugs.²¹ Moreover, pyridines are valuable in materials and surfaces,²² organocatalysis,²³ supramolecular structures,²⁴ and coordination chemistry.²⁵ Furthermore, these compounds serve as useful intermediates for preparing diverse heterocyclic compounds.²⁶

For the past few years, 2,3-dihydroquinazolin-4(1*H*)-one has gained considerable interest and has been utilized in preparing various drug molecules^{27,28} due to its potential biological and

^aDepartment of Chemistry, University of North Bengal, Dist. Darjeeling, West Bengal, India. E-mail: pizy12@yahoo.com; Fax: +91 353 2699001; Tel: +91 353 2776381

^bDepartment of Food Technology, University of North Bengal, Dist. Darjeeling, West Bengal, India

[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra09562a

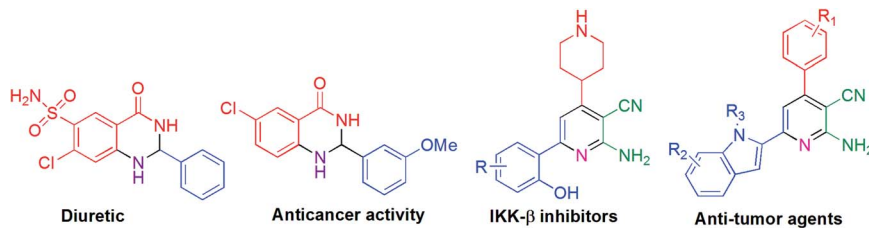



Fig. 1 Some bioactive molecules having 2-amino-3-cyanopyridine and 2,3-dihydroquinazolin-4(1*H*)-one skeleton.

pharmaceutical activities, which may be either antidepressant, analgesic, sedative, diuretic, or antihistamine.^{29–31} Anticancer activities, such as cell proliferation, inhibition of tubulin formation,³² and inhibition against VEGFR2 tyrosine kinase, are extraordinarily important features of these compounds. Plant growth regulatory³³ is another important activity of this molecule with a huge application. Some examples are given below in Fig. 1.

Many diverse protocols have been reported for synthesizing 2-amino-3-cyanopyridine derivatives such as Fe₃O₄,³⁴ acetic acid,³⁵ ultrasound irradiation,^{36,37} DMF,³⁸ Lewis acid catalysts,³⁹ and graphene oxide.⁴⁰ However, a straightforward and efficient one-pot reaction without a transition metal catalyst and hazardous solvent in mild conditions is still unexplored. Although several methods for preparing 2-amino-4,6-diphenylnicotinonitrile are well documented in the literature, most of them have a few limitations such as the use of hazardous solvents such as benzene or toluene, very high temperature, multiple-step pathway, long reaction times with low yields, use of transition metal that leads to metal contamination at the end of the reaction, and harsh reaction conditions that are not environmentally friendly.

Many strategies have been designed for synthesizing 2,3-dihydroquinazolin-4(1*H*)-ones in the literature; however, the most widely used method is the straightforward condensation reaction between 2-aminobenzamide and aldehyde. Most of these methodologies use metal salts,⁴¹ metal nano-particles⁴² of Co, Fe, La, Ag, In, and Cu, *p*-TSA,⁴³ amberlyst-15,⁴⁴ acidic silica,⁴⁵ trifluoroethanol,⁴⁶ cyanuric chloride,⁴⁷ heteropoly acid,⁴⁸ organic acid,⁴⁹ I₂,⁵⁰ NH₄Cl,⁵¹ and β-cyclodextrin.⁵² Synthesis of this molecule *via* a one-pot three-component protocol in a greener pathway is very tricky. Few methodologies for synthesizing 2,3-dihydroquinazolin-

4(1*H*)-one *via* a one-pot three-component strategy using aldehydes, isatoic anhydride, and amines are reported in the literature.⁵³ We have utilized the environmentally benign supramolecular catalyst β-cyclodextrin as a promoter for these two different one-pot multi-component organic reactions using aldehyde and ammonium acetate as the two main precursors (Schemes 1 and 2).

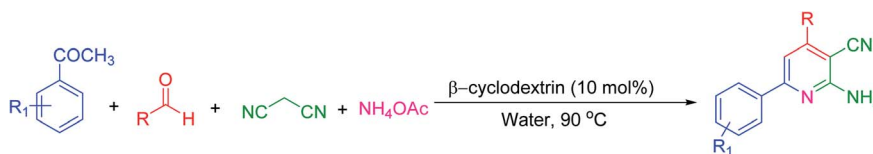
2. Experimental

2.1. Materials and apparatus

All compounds were purchased from commercial suppliers and used without further purification. ¹H NMR, ¹³C NMR, and ¹⁹F NMR were recorded using 300 MHz, 400 MHz and 75 MHz, 100 MHz and 376 MHz, respectively, on Bruker AV 300 NMR spectrometer and Bruker AV 400 NMR spectrometer using TMS as the internal standard. IR spectra were recorded on KBr disc in the range of 4000–400 cm⁻¹ on a Shimadzu FT-IR 8300 Spectrometer. The splitting patterns of protons were described as s (singlet), d (doublet), t (triplet), br (broad), and m (multiplet).

2.2. General procedure for the synthesis of 2-amino-4,6-disubstituted nicotinonitriles

β-Cyclodextrin (10 mol%) and water were added to a mixture of aromatic aldehydes (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol), and ammonium acetate (1 mmol) in a round-bottom flask. The resulting mixture was stirred at 90 °C for 2 h in the open air. The reaction progress was monitored using TLC with a mixture of ethyl acetate and *n*-hexane as the eluent system. After reaction completion, the mixture was quenched to room temperature and extracted with ethyl acetate



Scheme 1 One-pot four-component synthesis of 2-amino-4,6-diphenylnicotinonitriles.



Scheme 2 One-pot three-component synthesis of 2,3-dihydroquinazolin-4(1*H*)-one.



twice (2×20 ml). The combined extracts were washed with distilled water, dried over anhydrous Na_2SO_4 , and concentrated. The crude product was then purified by passing through a column packed with silica gel. The products obtained were known compounds and identified by melting points, FT-IR and ^1H , ^{13}C NMR spectroscopy.

2.3. General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones

Aldehydes (1 mmol), isatoic anhydride (1 mmol), and ammonium acetate (1 mmol) were added in a round-bottom flask and then β -cyclodextrin (10 mol%) was added to the mixture under a solvent-free condition. The resulting mixture was stirred at 90°C for 1 h in the open air. The reaction progress was monitored using TLC with a mixture of ethyl acetate and *n*-hexane as the eluent system. After reaction completion, the mixture was quenched to room temperature and extracted with ethyl acetate twice (2×20 ml). The combined extracts were washed with distilled water, dried over anhydrous Na_2SO_4 and concentrated. The residue obtained was recrystallized using a mixture of petroleum ether and ethyl acetate and then filtered to afford the desired pure solid products. All products were separated without column chromatography. The products obtained were known compounds and identified by melting point, FT-IR and ^1H , ^{13}C NMR spectroscopy.

2.4. Spectroscopic data of the synthesized compounds

2.4.1 2-Amino-4,6-diphenylpyridine-3-carbonitrile. Pale yellow solid; mp: 210°C ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ (ppm): 5.48 (s, 2H), 6.98 (d, $J = 7.8$ Hz, 2H), 7.20 (s, 1H), 7.40–7.47 (m,

3H), 7.68–7.82 (m, 3H), 8.14–8.26 (m, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ (ppm): 88.4, 110.0, 114.2, 117.8, 127.8, 129.4, 129.9, 130.3, 130.5, 138.1, 155.6, 158.8, 160.7, 161.9.

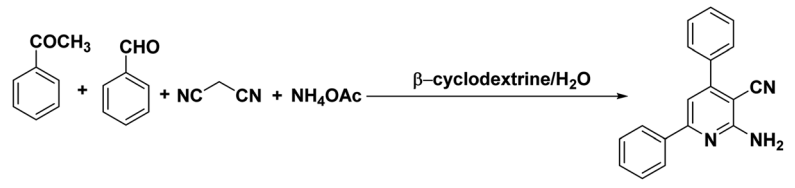
2.4.2 2-Amino-4-(4-methoxyphenyl)-6-phenylnicotinonitrile. Yellow solid; mp: 192 – 195°C ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.64 (s, 3H), 7.06 (d, $J = 7.8$ Hz, 2H), 7.20 (s, 1H), 7.42–7.68 (m, 3H), 7.65 (d, $J = 7.8$ Hz, 2H), 7.88 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ (ppm): 55.6, 86.9, 109.5, 114.6, 117.8, 127.7, 129.1, 129.5, 130.3, 130.5, 138.1, 154.9, 158.9, 160.8, 161.4.

2.4.3 2,3-Dihydro-2-phenylquinazolin-4(1H)-one. White solid; mp: 224 – 226°C ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 5.73 (s, 1H), 6.65 (t, $J = 7.6$ Hz, 1H), 6.72 (d, $J = 8$ Hz, 1H), 7.09 (s, 1H), 7.20–7.24 (m, 1H), 7.30–7.39 (m, 3H), 7.47 (d, $J = 8$ Hz, 2H), 7.59 (d, $J = 8$ Hz, 1H), 8.27 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ (ppm): 67.1, 114.9, 115.5, 117.6, 127.4, 127.9, 128.8, 129.0, 133.8, 142.1, 148.4, 164.1.

2.4.4 2,3-Dihydro-2-(4-methoxyphenyl)quinazolin-4(1H)-one. White solid; mp: 178 – 180°C ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 3.72 (s, 3H), 5.68 (s, 1H), 6.67 (t, $J = 7.6$ Hz, 1H), 6.71 (d, $J = 8$ Hz, 1H), 6.92 (d, $J = 8.8$ Hz, 2H), 6.98 (s, 1H), 7.21 (t, $J = 8.4$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.58 (d, $J = 8$ Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ (ppm): 55.4, 66.8, 114.1, 114.9, 115.5, 117.6, 127.8, 128.7, 133.7, 134.0, 148.5, 159.9, 164.2; IR (KBr) cm^{-1} : 757, 1251, 1505, 1654, 2363, 2922, 3295, 3424.

2.4.5 2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one. White solid; mp: 201 – 203°C ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 5.90 (s, 1H), 6.67 (t, $J = 7.6$ Hz, 1H), 6.76 (d, $J = 8$ Hz, 1H), 7.24 (t, $J = 7.6$ Hz, 1H), 7.31 (s, 1H), 7.60 (d, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 2H), 8.23 (d, $J = 8.8$ Hz, 2H), 8.51 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ (ppm): 65.8, 115.4, 118.0, 124.1, 126.4, 127.9, 128.5, 129.8, 134.1, 147.7, 149.8, 163.8.

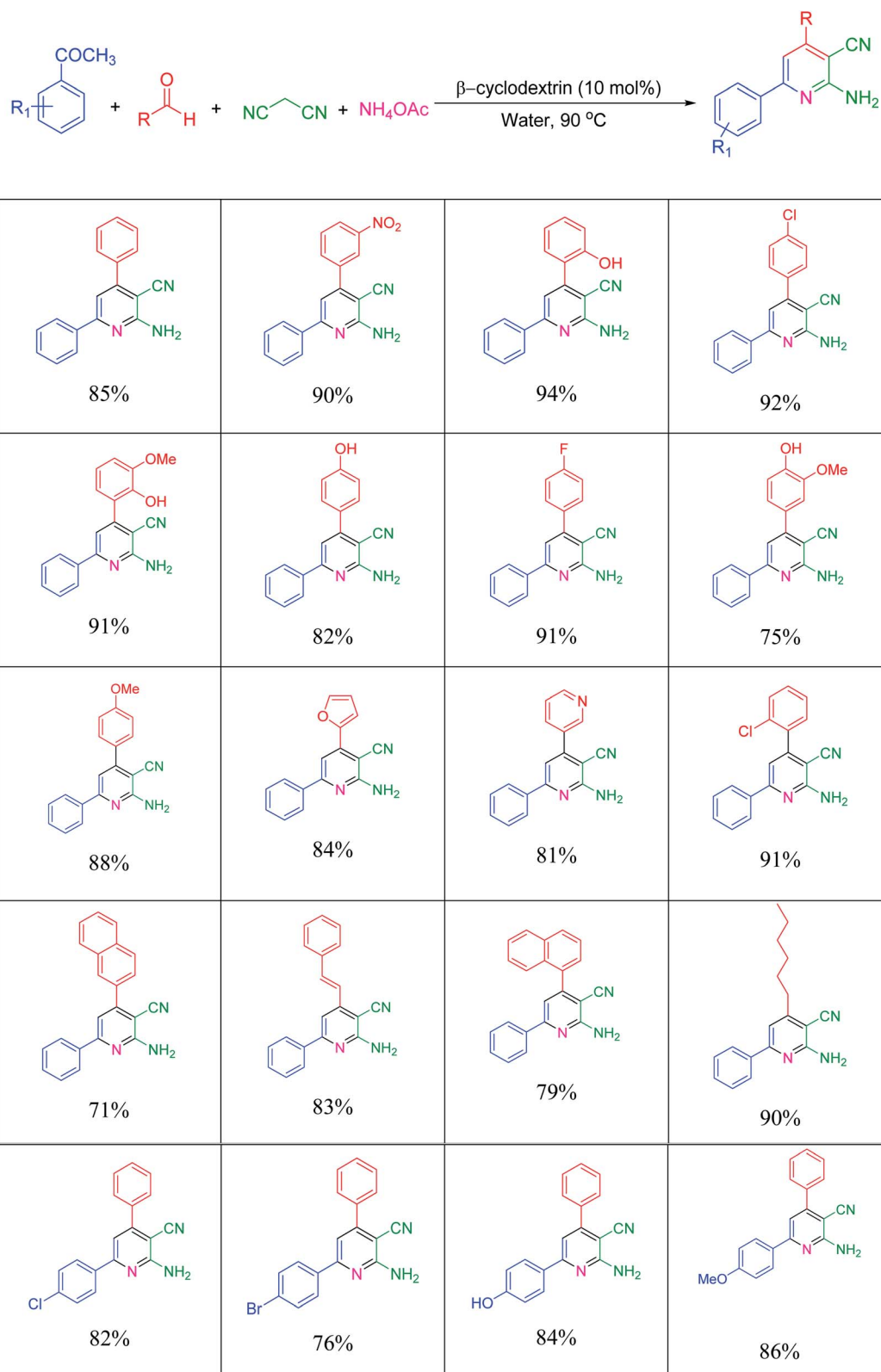
Table 1 Optimisation of the reaction parameters for 2-amino-4,6-diphenylnicotinonitriles^{a,b}



Entry	Catalyst (mol%)	Temperature ($^\circ\text{C}$)	Time (h)	Yield ^c (%)
1	30	90	8	88
2	20	90	8	86
3	10	90	8	86
4	10	90	2	84
5	10	90	1	74
6	5	90	8	62
7	4	90	8	40
8	2	90	8	Trace
9	—	90	12	—
10	10	50	2	73
11	10	Room temperature	12	68
12 ^d	10	90	2	Trace

^a The bold numbers represent the most optimized protocol/conditions. ^b Reaction of benzaldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol), and ammonium acetate (1 mmol) in water with β -cyclodextrin. ^c Isolated yield of the product by column chromatography. ^d Solvent-free reaction.



Table 2 Synthesis of certain diversified 2-amino-4,6-diphenylnicotinonitriles^a

^a Reaction condition: aldehyde (1 mmol), acetophenone (1 mmol), malononitrile (1 mmol), and ammonium acetate (1 mmol) in the presence of β -CD (10 mol%) in water at 90 °C for 2 h.



2.4.6 2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one.

White solid; mp: 202–204 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 5.73 (s, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8 Hz, 1H), 7.09 (s, 1H), 7.18–7.25 (m, 2H), 7.51–7.54 (m, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.29 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 66.5, 115.0, 115.6 (d, *J* = 21.5 Hz, 1C), 117.8, 127.9, 129.6 (d, *J* = 8.3 Hz, 1C), 133.9, 138.3 (d, *J* = 2.2 Hz, 1C), 148.3, 161.4, 163.8, 164.1; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ (ppm): –113.76 (s, 1F).

2.4.7 2,3-Dihydro-2-(thiophen-2-yl)quinazolin-4(1H)-one.

White solid; mp: 213–215 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ (ppm): 6.01 (s, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 6.96 (dd, *J* = 5.2 Hz & 3.6 Hz, 1H), 7.11 (s, 1H), 7.22–7.29 (m, 2H), 7.43 (dd, *J* = 4.8 Hz & 0.8 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.44 (s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ (ppm): 63.1, 115.2, 115.6, 118.0, 126.2, 126.4, 127.0, 127.8, 133.9, 146.9, 147.7, 163.6.

2.4.8 2,3-Dihydro-2-(pyridin-3-yl)quinazolin-4(1H)-one.

Pale yellow solid; mp: 219–221 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 5.85 (s, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 7.17 (s, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.40 (dd, *J* = 7.6 Hz & 4.8 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 8 Hz, 1H), 8.39 (s, 1H), 8.53 (d, *J* = 4 Hz, 1H), 8.66 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm): 65.2, 115.1, 115.5, 118.0, 124.1, 127.9, 134.0, 135.2, 137.3, 148.2, 148.9, 150.2, 164.1.

3. Results and discussion**3.1. Optimisation of reaction conditions**

To begin our study, we have taken benzaldehyde, acetophenone, malononitrile and ammonium acetate for a model reaction in the water medium. For the optimization of reaction conditions, parameters such as temperature, time and amount of catalyst were reported to have an influence on the reaction and it was monitored by TLC. Because β-cyclodextrin is soluble in water than any other organic solvent, we performed all reactions in water. The experimental results are summarized in

Table 1. Initially, the reaction was performed at 90 °C with 30 mol% of catalyst for 8 h, and 88% product was then formed (Table 1, entry 1). Then, we reduced the amount of the catalyst; when only 10 mol% of the catalyst was used, the yield was almost comparable with the yield of 30 mol% of catalyst (Table 1, entry 3). The same observation was seen in the case of optimization of time. By decreasing the time to 2 h, the yield was still 84% (Table 1, entry 4). Further decrease in the temperature (Table 1, entries 10, 11) and time (Table 1, entry 5) of the reaction did not increase the yield of the desired product. In the absence of a catalyst, no product was formed and only intermediates were formed, which was concluded by monitoring TLC (Table 1, entry 9). When we performed the same reaction in the solvent-free condition, a gummy solid was obtained (Table 1, entry 12). From this, it can be concluded that the reaction catalyzed by β-cyclodextrin and water is mandatory to perform the conversion.

Subsequently, the scope and efficiency of the reagent were explored under the optimized reaction conditions for the condensation of acetophenone with a broad range of structurally diverse aldehydes to furnish the related products. The structural diversity of the reactants is displayed in Table 2. The reactants bearing both electron-withdrawing and electron-donating substituents on the phenyl ring and the heterocyclic, aliphatic aldehydes are well tolerated under the reaction conditions to afford the final products in moderate to good yields (Table 2, entries 2–20). Electronic effects could be noticed in the reaction process. Aldehydes having electron-withdrawing groups give a better performance than those having electron-donating groups. Aldehydes having a hydroxyl group at the 2-position gave a better result, which may be attributed to H-bonding, whereas those with a hydroxyl group at the 4-position, the yield was moderate. Because of steric hindrance, 2-naphthylaldehyde moiety gave a better result than 1-naphthylaldehyde. 4-Substituted acetophenone gave a better result

Table 3 Screening of reaction conditions for 2,3-dihydroquinazolin-4(1H)-one derivatives^{a,b}

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield ^c (%)
1	20	90	5	92
2	10	90	5	90
3	5	90	5	78
4	2	90	8	Trace
5	—	90	8	—
6	10	90	1	90
7	10	50	2	74
8	10	rt	5	58

^a The bold numbers represent the most optimized protocol/conditions. ^b Reaction of isatoic anhydride (1 mmol), benzaldehyde (1 mmol), ammonium acetate (1 mmol), and β-cyclodextrin. ^c Isolated yield of the product by column chromatography.

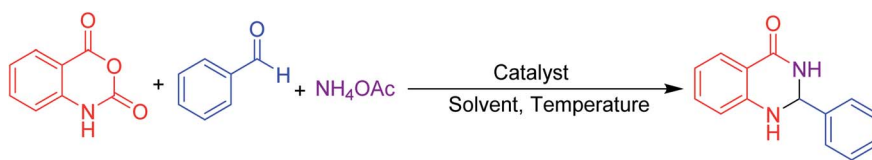
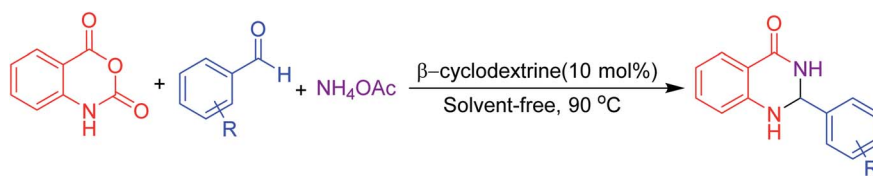


Table 4 Synthesis of the functionalized 2,3-dihydroquinazolin-4(1*H*)-one derivatives^a

Entry	Reactant	Product	Yield ^b (%)
1			90
2			84
3			88
4			78
5			92
6			75
7			89



Table 4 (Contd.)



Entry	Reactant	Product	Yield ^b (%)
8			90
9			86
10			72
11			79
12			83
13			80
14			92



Table 4 (Contd.)



Entry	Reactant	Product	Yield ^b (%)
15			95
16			84
17			89
18			93

^a Reaction of isoindolinone (1 mmol), aldehyde (1 mmol), and ammonium acetate (1 mmol) in the presence of β -CD (10 mol%) for 1 h at 90 °C under solvent-free condition. ^b Isolated yield of the product by column chromatography.

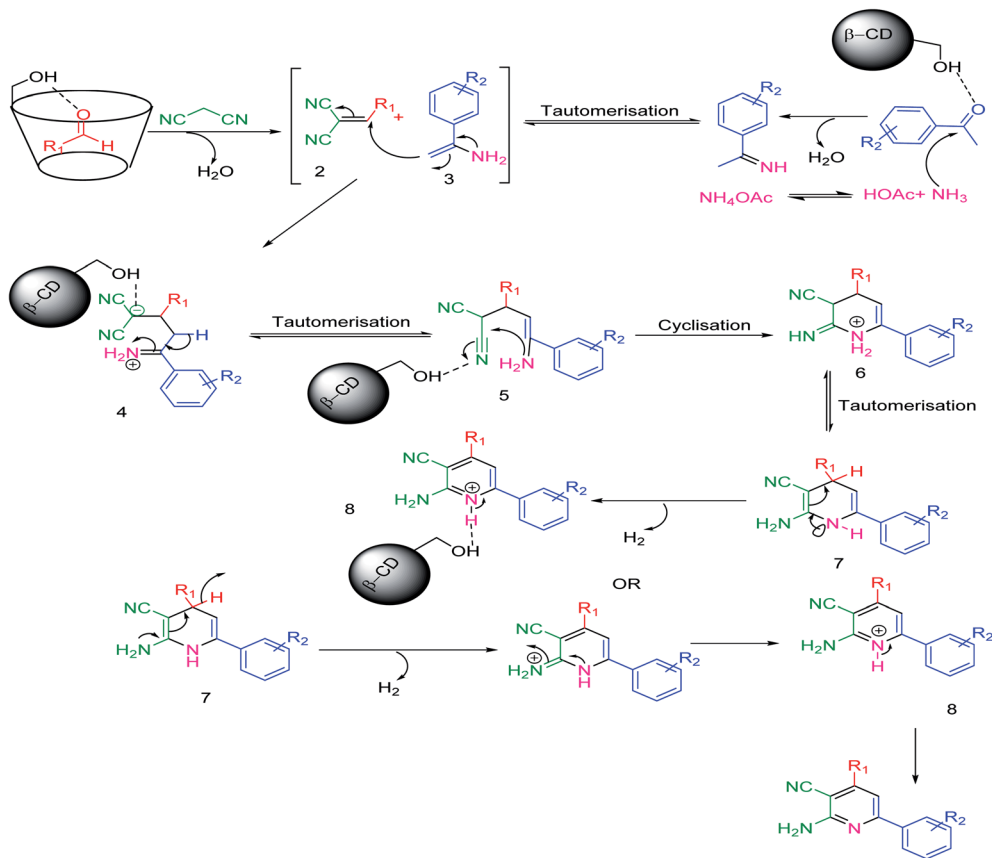
except for the amino group, which yielded only a trace product because of a self-condensation reaction.

For screening reaction conditions, isoindolinone, benzaldehyde and ammonium acetate are considered for the model reaction (Table 3). Reaction parameters such as temperature, time, solvent, and amount of catalyst showed a profound effect in performing the reaction, which was evident while monitoring the reaction using TLC. We started investigating the reaction under solvent-free condition using a different loading of catalyst. At first, we attempted the reaction with 20 mol% of catalyst per mmol of substrates at 90 °C where a good yield of the product was observed (Table 3, entry 1). We then started to reduce the amount of catalyst. Surprisingly, 10 mol% of catalyst at the same temperature yielded almost the same yield (Table 3, entry 2). Keeping the temperature constant and further reducing the amount of catalyst, the yield decreased (Table 3, entries 3, 4). Furthermore, in the absence of a catalyst, only the intermediate was formed, which was confirmed from TLC (Table 3,

entry 5). After fixing the amount of catalyst, we started to screen the time and temperature. With reduction in temperature to room temperature, the yield again decreased (Table 3, entries 7, 8). From this, temperature has considerable influence on this protocol. The further reduction of time from 5 h to 1 h with 10 mol% of catalyst loading at 90 °C yielded the same yield; therefore, 1 h may be enough to perform this protocol (Table 3, entry 6).

With these optimized reaction conditions, we tested the reactions with various aldehydes in Table 4, and all the aldehydes gave good yields. The aldehydes used were aromatic aldehydes having electron-withdrawing and electron-donating groups, aliphatic aldehyde (Table 4, entry 18), and five- and six-membered heterocyclic aldehydes (Table 4, entries 13, 14, 15, 16). The electron-withdrawing group in the benzene ring gave a slightly better yield than the electron-donating group. This may be due to the increase in the electrophilicity of carbonyl carbon of the aldehyde moiety. Substitution at the *ortho* position gave a poor yield than others, which may be due to the steric repulsion





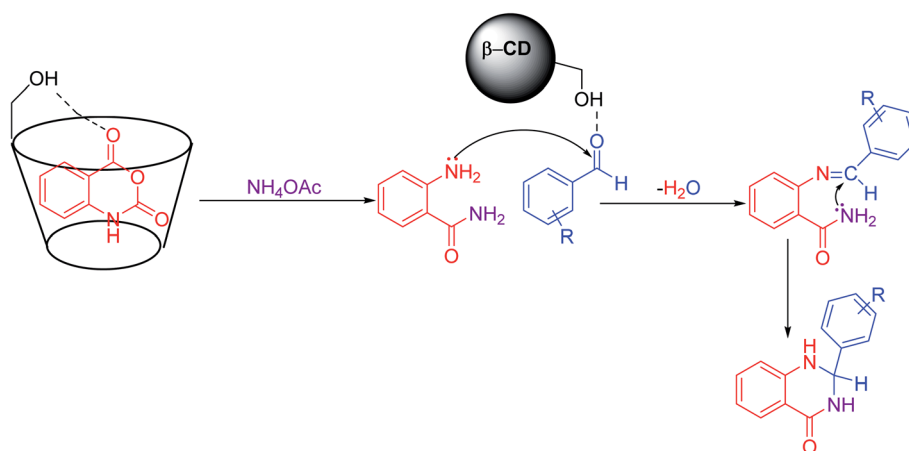
Scheme 3 Mechanism for the formation of the pyridine motif.

(Table 4, entries 6, 10). Amazingly, the hydroxyl group at the 2-position increased the yield than others, which may be due to its H-bonding effect (Table 4, entry 8).

3.2. Mechanism

A plausible mechanism⁵⁴ has been discussed in Scheme 3. β -CD with its seven free primary $-\text{OH}$ groups synergistically behaves as an efficient host and a supramolecular catalyst. β -CD, our potential catalyst, simultaneously activates both the aryl

aldehyde and acetophenone derivatives as the active electrophile species. The reaction of malononitrile and ammonium acetate with these two activated electrophiles generates the corresponding intermediates 2 and 3, respectively; intermediate 2 was then isolated. Afterwards, the reaction between these two intermediates will produce the corresponding intermediate 4. A sequence of tautomerization, cyclization, and again tautomerization generates the intermediate 7, which possesses a structure having a lone pair on the nitrogen atom sharing electrons from both $-\text{NH}_2$ and $-\text{NH}$ functional groups through $\text{C}=\text{C}$



Scheme 4 Mechanism for the formation of the 2,3-dihydroquinazolin-4(1H)-ones.



double bonds in the presence of the described catalyst and yields the desired products.

A plausible mechanism was described for synthesizing 2,3-dihydroquinazolin-4(1*H*)-one (Scheme 4). In the first step, isatoic anhydride coordinates to the β -CD cavity; by the reaction of ammonium acetate, it forms 2-aminobenzamide as an intermediate, which is then isolated. In the next step, it facilitates the nucleophilic attack by the electron-rich nitrogen of the amine group to the electrophilic carbonyl carbon centre of aldehydes, which is activated by β -CD. Then, the elimination of water followed by another nucleophilic attack by the amine group of the amide to the carbon centre on the substituted imine leads to the expected product 2,3-dihydroquinazolin-4(1*H*)-one.

4. Conclusion

In conclusion, we have developed a straightforward, robust and facile eco-friendly strategy for preparation of 2-amino-4,6-diphenylnicotinonitrile and 2,3-dihydroquinazolin-4(1*H*)-one derivatives using a bio-based supramolecule, β -cyclodextrin, in water and solvent-free condition, respectively, without using any additional catalyst or metal salt, which further enhances the advantage of the protocol. The replacement of toxic and expensive metal catalysts by an environment-friendly and inexpensive organocatalyst is the novelty of this protocol. This environmentally benign protocol is expected to achieve wide applications in the pharmaceutical industry and natural product synthesis.

Author contributions

BM and GCP contribute equally to these methodologies. Scheme 1 is done by BM, and Scheme 2 is done by GCP under the guidance of Prof. P. Ghosh.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

B. M. is thankful to CSIR, New Delhi for financial support.

References

- 1 Y. A. Tayade, A. D. Jangale and D. S. Dalal, *ChemistrySelect*, 2018, **3**, 8895–8900.
- 2 (a) P. Basak, S. Dey and P. Ghosh, *ChemistrySelect*, 2020, **5**, 626–636; (b) R. Singha, P. Basak, M. Bhattacharya and P. Ghosh, *ChemistrySelect*, 2020, **5**, 6514–6525; (c) P. Basak and P. Ghosh, *Synth. Commun.*, 2018, **48**, 2584–2599; (d) G. C. Pariyar, B. Mitra, S. Mukherjee and P. Ghosh, *ChemistrySelect*, 2020, **5**, 104–108.
- 3 (a) S. S. Reddy, M. V. K. Reddy and P. V. G. Reddy, *ChemistrySelect*, 2018, **3**, 4283–4288; (b) S. N. Murthy and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2011, **52**, 4481–4484; (c) M. Abbasi, *J. Chin. Chem. Soc.*, 2017, **64**, 896–917; (d) S. V. Akolkar, N. D. Kharat and A. A. Nagargoje, *Catal. Lett.*, 2020, **150**, 450–460; (e) A. Ghorad, S. Mahalle and L. D. Khillare, *Catal. Lett.*, 2017, **147**, 640–648; (f) G. Dhananjaya, A. V. D. Rao, K. A. Hossain, V. R. Anna and M. Pal, *Tetrahedron Lett.*, 2020, **61**, 151972, DOI: 10.1016/j.tetlet.2020.151972; (g) Y. A. Tayade, S. A. Padvi, Y. B. Wagh and D. S. Dalal, *Tetrahedron Lett.*, 2020, **56**, 2441–2447.
- 4 L. R. Reddy, N. Bhanumathi and K. R. Rao, *Chem. Commun.*, 2000, 2321–2322.
- 5 M. A. Reddy, N. Bhanumathi and K. R. Rao, *Chem. Commun.*, 2001, 1974–1975.
- 6 K. Surendra, N. S. Krishnaveni, R. Sridhar and K. R. Rao, *Tetrahedron Lett.*, 2006, **47**, 2125–2127.
- 7 O. Z. Tee, C. Mazza, R. Lozano Hemmer and J. B. Giorgi, *J. Org. Chem.*, 1994, **59**, 7602–7608.
- 8 L. Marchetti and M. Levine, *ACS Catal.*, 2011, **1**, 1090–1118.
- 9 R. Breslow and U. Maitra, *Tetrahedron Lett.*, 1983, **24**, 1901–1904.
- 10 A. Gonzalez and S. Holt, *J. Org. Chem.*, 1982, **47**, 3186–3188.
- 11 H. J. Schneider and N. K. Sangwan, *J. Chem. Soc., Chem. Commun.*, 1986, **24**, 1787–1789.
- 12 D. D. Sternbach and D. M. Rossana, *J. Am. Chem. Soc.*, 1982, **104**, 5853–5854.
- 13 A. L. Laza Knoerr, R. Gref and P. J. Couvreur, *J. Drug Targeting*, 2010, **18**, 645–656.
- 14 J. Heng-Bing, S. DongPo, S. Ming, L. Zhong, W. Le-Fu, H. B. Ji, D. P. Shi, M. Shao, Z. Li and L. F. Wang, *Tetrahedron Lett.*, 2005, **46**, 2517–2520.
- 15 (a) P. Choudhury, P. Ghosh and B. Basu, *Mol. Diversity*, 2020, **24**, 283–294; (b) B. Mitra, S. Mukherjee, G. C. Pariyar and P. Ghosh, *Tetrahedron Lett.*, 2018, **59**, 1385–1389.
- 16 T. Murata, M. Shimada, S. Sakakibara, T. Yoshino, H. Kadono, T. Masuda, M. Shimazaki, T. Shintani, K. Fuchikami, K. Sakai, H. Inbe, K. Takeshita, T. Niki, M. Umeda, K. B. Bacon, K. B. Ziegelbauer and T. B. Lowinger, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 913–918.
- 17 M. Mantri, O. De Graaf, J. Van Veldhoven, A. Göblyös, J. K. Von Frijtag Drabbe Künzel, T. Mulder-Krieger, R. Link, H. De Vries, M. W. Beukers, J. Brussee and A. P. Ijzerman, *J. Med. Chem.*, 2008, **51**, 4449–4455.
- 18 J. Deng, T. Sanchez, L. Q. Al-Mawsawi, R. Dayam, R. A. Yunes, A. Garofalo, M. B. Bolger and N. Neamati, *Bioorg. Med. Chem.*, 2007, **15**, 4985–5002.
- 19 H. M. Kanjariya, T. V. Radhakrishnan, K. R. Ramchandran and P. Hansa, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2004, **43**, 1569–1573.
- 20 J. Stoltefuss, S. Goldmann, A. Straub, H. Boeshagen, M. Bechem, R. Gross, S. Hebisch, J. Huetter and H. P. Rounding, *US Pat.*, 5432282, 1995.
- 21 T. Murata, M. Shimada, H. Kadono, S. Sakakibara, T. Yoshino, T. Masuda, M. Shimazaki, T. Shintani, K. Fuchikami, K. B. Bacon and T. B. Z. Lowinger, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4013–4017.
- 22 R. Makiura, S. Motoyama, Y. Umemura, H. Yamanaka, O. Sakata and H. Kitagawa, *Nat. Mater.*, 2010, **9**, 565–571.
- 23 N. De Rycke, F. Couty and O. R. P. David, *Chem.–Eur. J.*, 2011, **17**, 12852–12871.



- 24 T. Šmejkal and B. Breit, *Angew. Chem., Int. Ed.*, 2008, **47**, 311–315.
- 25 D. Bora, B. Deb, A. L. Fuller, A. M. Z. Slawin, J. D. Woollins and D. K. Dutta, *Inorg. Chim. Acta*, 2010, **363**, 1539–1546.
- 26 C. J. Shishoo, M. B. Devani, V. S. Bhadti, S. Ananthan and G. V. Ullas, *Tetrahedron Lett.*, 1983, **24**, 4611–4612.
- 27 J. F. Wolfe, T. L. Rathman, M. C. Sleevi, J. A. Campbell and T. D. Greenwood, *J. Med. Chem.*, 1990, **33**, 161–166.
- 28 J. K. Padia, M. Field, J. Hinton, K. Meecham, J. Pablo, R. Pinnock, B. D. Roth, L. Singh, N. Suman-Chauhan, B. K. Trivedi and L. Webdale, *J. Med. Chem.*, 1998, **41**, 1042–1049.
- 29 E. Hamel, C. M. Lin, J. Plowman, H. Wang and K. D. Pad, *Biochem. Pharmacol.*, 1996, **51**, 53–59.
- 30 J. A. Lowe, R. L. Archer, D. S. Chapin, J. B. Cheng, D. Helweg, J. L. Johnson, B. K. Koe, L. A. Lebel and P. F. Moore, *J. Med. Chem.*, 1991, **34**, 624–628.
- 31 H. J. Havera, *J. Med. Chem.*, 1979, **22**, 1548–1550.
- 32 G. Wagner and I. Wunderlich, *Pharmazie*, 1978, **33**, 15.
- 33 C. H. Boehringer Sohn, *Chem. Abstr.*, 1964, **61**, 16075h.
- 34 M. M. Heravi, S. Y. S. Beheshtiha, M. Dehghani and N. Hosseintash, *J. Iran. Chem. Soc.*, 2015, **12**, 2075–2081.
- 35 A. N. Vasiliev, Y. S. Kayukov, O. E. Nasakin, A. N. Lyshchikov, V. N. Nesterov, O. V. Kayukova and O. V. Poulkherovskaya, *Chem. Heterocycl. Compd.*, 2011, **37**, 309–314.
- 36 F. Shi, V. Tu, F. Fang and T. Li, *ARKIVOC*, 2005, 137–142.
- 37 W. J. Zhou, S. J. Ji and Z. L. Shen, *J. Organomet. Chem.*, 2006, **691**, 1356–1360.
- 38 A. M. Shestopalov and O. A. Naumov, *Russ. Chem. Bull.*, 2003, **52**, 1380–1385.
- 39 J. Tang, L. Wang, Y. Yao, L. Zhang and W. Wang, *Tetrahedron Lett.*, 2011, **52**, 509–511.
- 40 D. Khalili, *Tetrahedron Lett.*, 2016, **57**, 1721–1723.
- 41 (a) J. X. Chen, D. Z. Wu, F. He, M. C. Liu, H. Y. Wu, J. C. Ding and W. K. Su, *Tetrahedron Lett.*, 2019, **49**, 3814–3818; (b) D. Zhan, T. Li, H. Wei, W. Weng, K. Ghandi and Q. Zeng, *RSC Adv.*, 2013, **3**, 9325–9329; (c) J. X. Chen, H. Y. Wu and W. K. Su, *Chin. Chem. Lett.*, 2007, **18**, 536–538; (d) M. Prakesh and V. Kesavan, *Org. Lett.*, 2012, **7**, 1896–1899; (e) R. J. Abdel, W. Voelter and M. A. Saeed, *Tetrahedron Lett.*, 2004, **45**, 3475–3476; (f) G.-P. Cai, X.-L. Xu, Z.-F. Li, P. Willam, P. Weber and J. Lu, *J. Heterocycl. Chem.*, 2002, **39**, 1271–1272; (g) C. L. Yoo, J. C. Fettinger and M. J. Kurth, *J. Org. Chem.*, 2005, **70**, 6941–6943; (h) A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Biomol. Chem.*, 2012, **10**, 240–243; (i) J. Zhou and J. Fang, *J. Org. Chem.*, 2011, **76**, 7730–7736; (j) H. Li, L. He, H. Neumann, M. Beller and X.-F. Wu, *Green Chem.*, 2014, **16**, 1336–1343; (k) H. Hikawa, Y. Ino, H. Suzuki and Y. Yokoyama, *J. Org. Chem.*, 2012, **77**, 7046–7051; (l) X. Jiang, T. Tang, J.-M. Wang, Z. Chen, Y.-M. Zhu and S.-J. Ji, *J. Org. Chem.*, 2014, **79**, 5082–5087; (m) M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary and A. A. Mohammadi, *Tetrahedron Lett.*, 2005, **46**, 6123–6126; (n) D. Shi, L. Rong, J. Wang, Q. Zhuang, X. Wang and H. Hu, *Tetrahedron Lett.*, 2003, **44**, 3199–3201.
- 42 (a) J. Safari and S. G. Ravandi, *C. R. Chim.*, 2013, **16**, 1158–1164; (b) A. G. Choghmarani and M. Norouzi, *J. Mol. Catal. A: Chem.*, 2014, **395**, 172–179; (c) J. Safari and S. Gandomi-Ravandi, *J. Mol. Catal. A: Chem.*, 2013, **371**, 135–140; (d) J. Safari and S. G. Ravandi, *RSC Adv.*, 2014, **4**, 11654–11660; (e) S. Santra, M. Rahman, A. Roy, A. Majee and A. Hajra, *Catal. Commun.*, 2014, **49**, 52–57; (f) S. Tarannum, N. Ahmed and Z. N. Siddiqui, *Catal. Commun.*, 2015, **66**, 60–66; (g) A. G. Choghmarani and G. Azadi, *RSC Adv.*, 2015, **5**, 9752–9756.
- 43 R. Cheng, T. Guo, D. Zhang-Negrerie, Y. Du and K. Zhao, *Synthesis*, 2013, **45**, 2998–3006.
- 44 P. V. Murthy, D. Rambabu, G. RamaKrishna, C. M. Reddy, K. R. Prasad, M. V. B. Rao and M. Pal, *Tetrahedron Lett.*, 2012, **53**, 863–867.
- 45 M. Dabiri, P. Salehi, M. Baghbanzadeh, M. A. Zolfigol, M. Agheb and S. Heydari, *Catal. Commun.*, 2008, **9**, 785–788.
- 46 (a) R. Z. Qiao, B. L. Xu and Y. H. Wang, *Chin. Chem. Lett.*, 2007, **18**, 656–658; (b) P. Salehi, M. Dabiri, M. A. Zolfigol and M. Baghbanzadeh, *Synlett*, 2019, 1155–1157.
- 47 M. Sharma, S. Pandey, K. Chauhan, D. Sharma, B. Kumar and P. M. Chauhan, *J. Org. Chem.*, 2012, **77**, 929–937.
- 48 Y.-X. Zong, Y. Zhao, W.-C. Luo, X. H. Yu, J.-K. Wang and Y. Pan, *Chin. Chem. Lett.*, 2010, **21**, 778–781.
- 49 G. C. Pariyar, B. Mitra, S. Mukherjee and P. Ghosh, *ChemistrySelect*, 2020, **5**, 104–108.
- 50 (a) S. Rostamizadeh, A. M. Amani, R. Aryan, H. R. Ghaieni and N. Shadjou, *Synth. Commun.*, 2008, **38**, 3567–3576; (b) X. S. Wang, K. Yang, J. Zhou and S. J. Tu, *J. Comb. Chem.*, 2010, **12**, 417–421.
- 51 A. Shaabani, A. Maleki and H. Mofakham, *Synth. Commun.*, 2008, **38**, 3751–3755.
- 52 K. Ramesh, K. Karnakar, G. Satish, B. S. P. Anil Kumar and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2012, **53**, 6936–6939.
- 53 (a) R. Sharma, A. K. Pandey and P. M. S. Chauhan, *Synlett*, 2012, **23**, 2209–2214; (b) F. Tamaddon and M. T. K. Varnamkhasti, *Synlett*, 2016, **27**, 2510–2514; (c) Z.-H. Zhang, H.-Y. Lü, S.-H. Yang and J.-W. Gao, *J. Comb. Chem.*, 2010, **12**, 643–646; (d) C. K. Khatri, M. S. Patil and G. U. Chaturbhuj, *J. Iran. Chem. Soc.*, 2017, **14**, 1683–1689; (e) N. Razavi and B. Akhlaghinia, *New J. Chem.*, 2016, **40**, 447–457; (f) S. Zhaleh, N. Hazeri and M. T. Maghsoudlou, *Res. Chem. Intermed.*, 2016, **42**, 6381–6390; (g) S. Karhale, D. Survase and R. Bhat, *Res. Chem. Intermed.*, 2017, **43**, 3915–3924; (h) A. Sahu, S. Mishra, P. Sahu, A. Gajbhiye and R. K. Agrawal, *Curr. Organocatal.*, 2018, **5**, 137–144; (i) S. J. Wu, Z. Q. Zhao and J. S. Gao, *Res. Chem. Intermed.*, 2019, **45**, 2327–2339; (j) F. Tamaddon and M. T. K. Varnamkhasti, *Synlett*, 2016, **27**, 2510–2514; (k) Y. Yang, R. Fu, Y. Liu, J. Cai and X. Zeng, *Tetrahedron*, 2020, **76**, 131312; (l) J. Wu, X. Du, J. Ma, Y. Zhang, Q. Shi, L. Luo, B. Song, S. Yanga and D. Hu, *Green Chem.*, 2014, **16**, 3210–3217; (m) D. R. Patil, P. G. Ingole, K. Singh and D. S. Dalal, *J. Inclusion Phenom. Macrocyclic Chem.*, 2013, **76**, 327–332.
- 54 M. A. Zolfigol, M. Kiafar, M. Yarie, A. Taherpour, T. Fellowes, A. N. Hancock and A. Yari, *J. Mol. Struct.*, 2017, **1137**, 674–680.

