RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2016, **6**, 22034

Merging supramolecular catalysis and aminocatalysis: amino-appended β-cyclodextrins (ACDs) as efficient and recyclable supramolecular catalysts for the synthesis of tetraketones†

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Received 12th January 2016
Accepted 16th February 2016

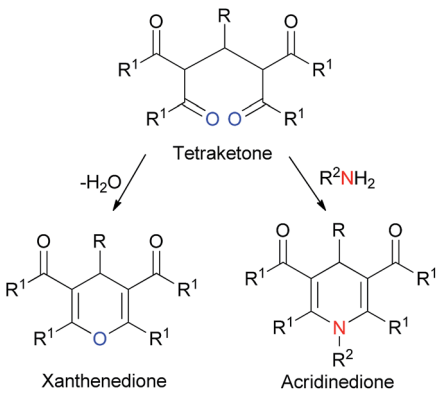
DOI: 10.1039/c6ra01002d

www.rsc.org/advances

Well-designed amino-appended β-cyclodextrins (ACDs) with an amino side chain of different lengths at the primary face of β-CD were synthesized and employed in the catalytic synthesis of a series of tetraketones as supramolecular catalysts in water for the first time. Yields of 58–97% were obtained with up to 30 examples of substrate. The catalyst could be recycled easily, while a 92% yield and 84% rate of catalyst recovery could be achieved after 8 cycles of catalyst recycling. Moreover, a catalytic mechanism merging supramolecular catalysis and aminocatalysis could be proposed through detailed 1D and 2D NMR, ESI-MS and Job plot analyses. This protocol retained the promising characteristics of ambient temperature, green medium, simple operation, broad substrate scope, excellent yields, superb catalyst recycling performance and unique catalytic mechanism.

Introduction

Tetraketones are organic multifunctional molecules with four carbonyl groups. Since the first synthesis of tetraketones reported by Merling in 1894,[1] they have exhibited important biological activities such as tyrosinase inhibition,[2] lipoxygenase inhibition[3,4] and antioxidant activities.[3–5] In addition to that, tetraketones have been frequently used as important precursors for the synthesis of biologically important heterocyclic compounds such as xanthenediones[6] and acridinediones (Scheme 1).[7–10]



Scheme 1 Tetraketone and its derivatives.

Due to the biological and chemical importances of tetraketones, synthesis of such molecules has provoked more and more interests of chemists. Varies of synthetic methods were reported involving

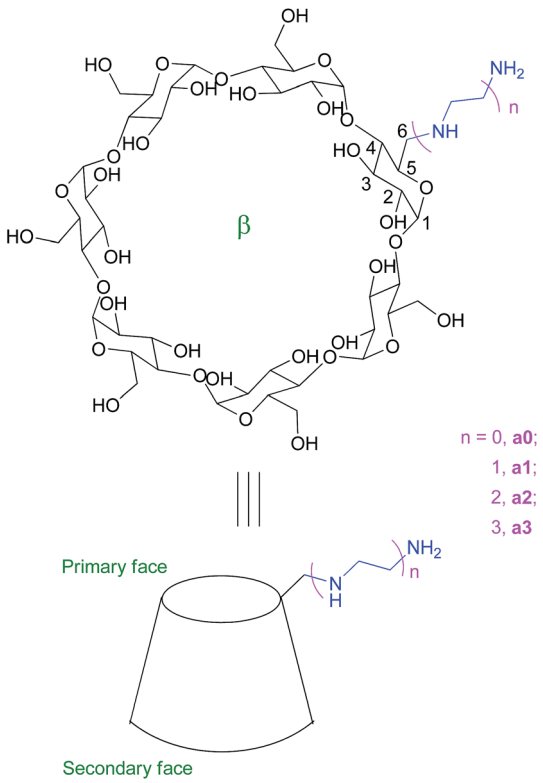


Fig. 1 The structure of ACDs.

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† Electronic supplementary information (ESI) available: Spectral data of catalysts and products. See DOI: 10.1039/c6ra01002d

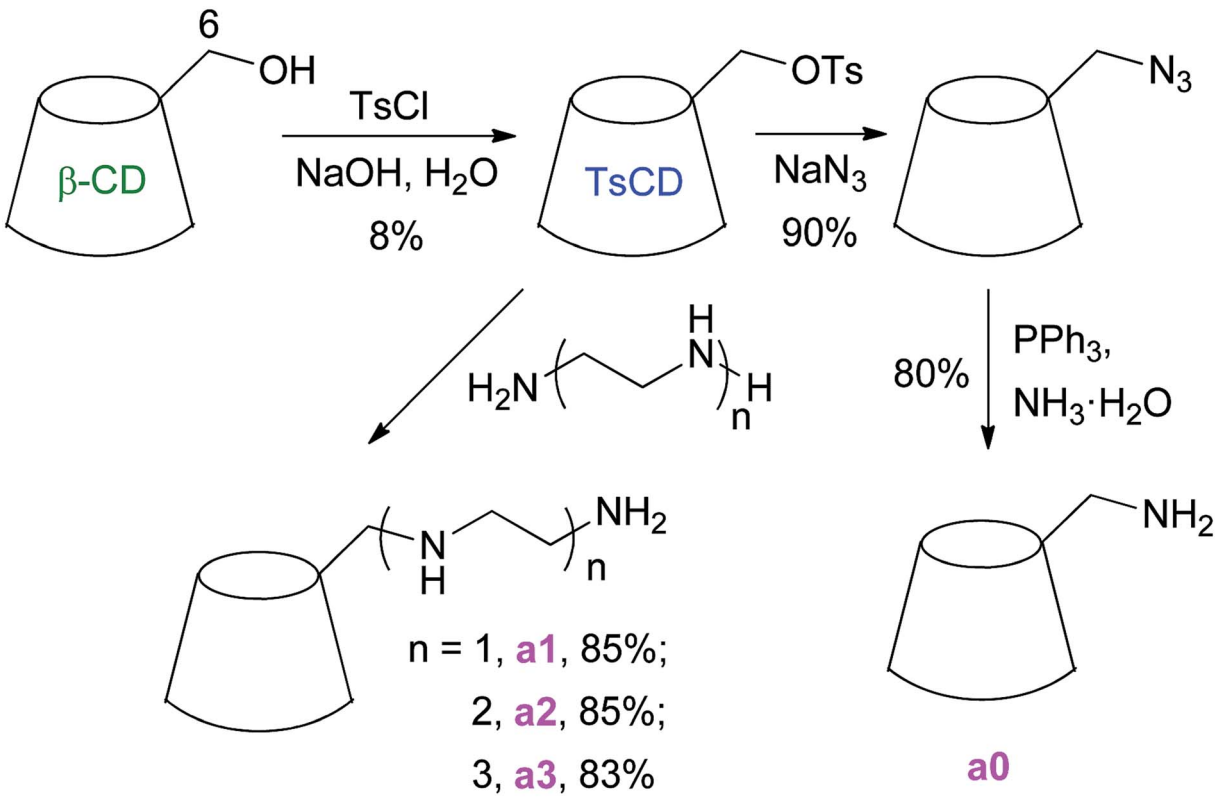
pyridine,[2] TEAB,[3] In(OTf),[3,5] metal hydroxides,[11,12] L-proline,[13] molecular iodine,[14] $HClO_4$–SiO_2,[15] nickel nanoparticles,[16] choline chloride[17] and nano SiO_2Cl (ref. 18) as catalysts or without any catalyst.[19] Nevertheless, more efficient and environmentally benign approaches to tetraketones are still in demand.

Cyclodextrins (CDs) are a family of oligosaccharides which are usually composed of 6, 7 or 8 D-glucose monomers linked by α-1,4-glycosidic bonds, referred to as α-, β- and γ-CD respectively.[20,21] In terms of their virtues of aqueous solubilities, low toxicities and biodegradability, CDs are widely utilized in chemical, food, cosmetics and pharmaceutical fields.[22–25] CDs have hydrophilic outer shell and hydrophobic inner cavity, which could encapsulate guest molecules to form host–guest inclusion complexes. Water insoluble drug molecules could improve their physicochemical properties such as water solubility, stability, bioavailability and even targeted drug delivery performance by formation of inclusion complexes with CDs.[26–33] In the field of organic synthesis, CDs also play a remarkable role as supramolecular catalysts in various catalytic transformations such as oxidation, reduction, hydrolysis and condensation, *etc.*[34–41] Among CD catalysts, β-CD is the most popular one due to its readiest availability. However, catalytic reactions using native β-CD have been severely limited by its relatively low water solubility and functional homogeneity. Chemical modification of β-CD has emerged as an effective approach to addressing this issue. Inspired by the powerful organocatalysis with amines in recent decades,[42–46] we designed to combine the power of supramolecular catalysis and aminocatalysis by construction of amino-appended β-CD (ACD) catalysts.

Recently, β-CD catalysts modified with amino groups were employed in catalytic reactions such as oxidation,[47] addition,[48–51] selective protection of amines,[52] cross-couplings[53,54] and synthesis of heterocyclic compounds.[55–57] However, the types of amino-containing groups appended to β-CD remain very limited to date, which has severely hampered their applications. Thus newly designed ACDs are in urgent need and are of great challenge. Considering the potential unique reaction mode inside the CD cavity accompanied by possible self-inclusion between CD and amino side chains of appropriate lengths[58] and its impact on catalytic performance, ACDs (Fig. 1) with amino side chains of different lengths were designed and synthesized and their performances on catalytic synthesis of tetraketones were evaluated.

Results and discussion

The ACDs were prepared by concise procedures as shown in Scheme 2. Mono-6-(4-tolunesulfonyl)-6-deoxy-β-CD (TsCD) was first synthesized using 4-tolunesulfonyl chloride (TsCl) in an aqueous solution of sodium hydroxide. Catalyst **a0** was obtained *via* a two-step sequence of azide replacement and then Staudinger reduction from TsCD. On the other hand, catalysts **a1–a3** were prepared by nucleophilic substitution on TsCD with specific amino compounds.



Scheme 2 Preparation of ACDs.

The obtained ACDs were subsequently thrown in the catalytic synthesis of tetraketones. The optimization of reaction conditions was performed with benzaldehyde and dimedone in water at room temperature (Table 1). β-CD could give the highest yield (73%) among α-, β- and γ-CD with a 5 mol% catalyst loading (entries 2–4), equaling to that without no catalysts (entry 1). Moderate yields were obtained when alkali metal salts (entries 5–7) or ammonium phase-transfer catalysts (entries 8 & 9) were used, while natural amino acids gave only low to moderate yields (entries 10–12). When ACDs were employed in this reaction, yields were promoted significantly, up to 81%, 80%, 90% and 92% with catalysts **a0–a3**, respectively (entries 13–16). Neither increasing nor decreasing the catalyst loading of **a3** (to 2% or 10%) did bring benefit to the yield (entries 17 & 18). However, it rose to 96% when reducing the reaction time from 5 h to 1 h (entry 19), and fell down to 79% when further decreasing to 0.5 h (entry 20). Noticeably, the reaction temperature was found to play a crucial role on this reaction for the yield declined sharply as cooled to 0 °C (entry 21), which could be attributed to the decreased water solubility of **a3** at such a low temperature. On the contrary, moderate to good yields could be obtained at higher temperatures (entries 22 & 23). Significant solvent effects were also observed while it gave 40% and 92% yields in ethanol and DMF respectively (entries 24 & 25), as DMF was normally a superior solvent like water for ACDs.

The best catalytic potency of catalyst **a3** in water could be supported by the evidence that it had superior water solubility of up to 656.9 mg mL^{-1}, which was also the best among ACDs (see ESI†).

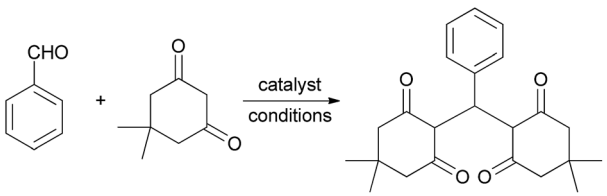
With the optimized conditions in hand, the substrate scope was explored (Table 2). Reaction of dimedone with substituted benzaldehydes with either electro-donating or withdrawing groups all gave excellent yields of expected products (85–95%, entries 2–15), as well as naphthaldehyde and heterocyclic aromatic aldehydes (92–96%, entries 16–18). Two benzenedicarboxaldehydes were also screened and both gave high yields (entries 19 & 20). Aliphatic aldehydes including acyclic and cyclic ones were also found to be expedient substrates for this reaction (92–97%, entries 21–27). Besides, 7-fluoroisatin as an aldehyde analogue gave moderate yield (entry 28). Moreover, reactions of benzaldehyde with 1,3-cyclohexanedione or 4-hydroxy-6-methyl-2*H*-pyran-2-one gave very good yields (entries 29 & 30) as well.

The reaction mechanism was then extensively studied by spectroscopic analyses. The formation of inclusion complexes of ACDs with substrates was demonstrated by ^{1}H NMR spectra of **a3**, **a3**/4-nitrobenzaldehyde complex and freeze-dried reaction mixture of **a3**/4-nitrobenzaldehyde/dimedone in D_2O (Table 3). It was observed that downfield shifts of H-3 (0.011 ppm) and H-5 (0.004 ppm) protons of **a3**/4-nitrobenzaldehyde complex (B) occurred compared to that of **a3** (A), which indicated the formation of inclusion complex of 4-nitrobenzaldehyde with **a3**. Further study on the ^{1}H NMR spectra of the freeze-dried reaction mixture of **a3**/4-nitrobenzaldehyde/dimedone (C) revealed that there were significant upfield shifts of H-3 (0.057 ppm), H-5 (0.088) and H-6 (0.034 ppm) compared to that of **a3** (A). This indicated that dimedone was likely to react with 4-nitrobenzaldehyde by condensation inside the cavity of **a3**.

In order to further explore the possible interacting mode of catalyst **a3** with substrates, the ROESY of the reaction mixture of **a3**/4-nitrobenzaldehyde/dimedone was recorded in D_2O (Fig. 2). It showed appreciable correlation of aromatic protons (H_o, H_m) of 4-nitrobenzaldehyde with inner protons (H-3, H-5) of **a3**, namely, H_m correlated with both H-3 and H-5, while H_o only correlated with H-3 (Fig. 2(A)). Considering that H-3 is located at the side of the secondary face of **a3**, this suggested the probably spatial layout of 4-nitrobenzaldehyde in the cavity of **a3** with the carbonyl group near to the secondary face of **a3**. Besides, there were significant correlations between the ethylene protons (H-en) of the amino side chain of **a3** with H-3 and H-5 (Fig. 2(B)), which were consistent with that of native **a3** (see ESI†). This indicated that the amino side chain inserted inside the cavity of **a3** during the reaction.

Furthermore, electrospray ionization mass spectrometry (ESI-MS) analysis of **a3**/4-nitrobenzaldehyde complex was used

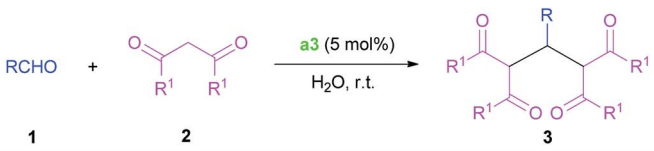
Table 1 The optimization of reaction conditions[a]

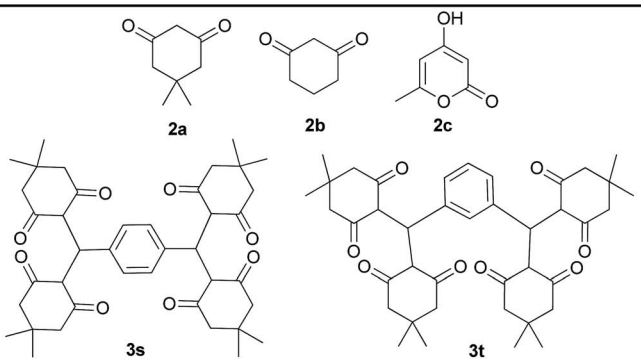


Entry	Catalyst (mol%)	Time (h)	Temp (°C)	Yield[b] (%)
1	None	5	r.t.	73
2	α-CD (5)	5	r.t.	43
3	β-CD (5)	5	r.t.	73
4	γ-CD (5)	5	r.t.	41
5	NaCl (5)	5	r.t.	53
6	NaBr (5)	5	r.t.	60
7	KBr (5)	5	r.t.	63
8	TBAC[c] (5)	5	r.t.	72
9	TEAI[d] (5)	5	r.t.	76
10	L-Proline (5)	5	r.t.	75
11	L-Cysteine (5)	5	r.t.	22
12	L-Aspartic acid (5)	5	r.t.	58
13	**a0** (5)	5	r.t.	81
14	**a1** (5)	5	r.t.	80
15	**a2** (5)	5	r.t.	90
16	**a3** (5)	5	r.t.	92
17	**a3** (2)	5	r.t.	89
18	**a3** (10)	5	r.t.	90
19	**a3** (5)	**1**	**r.t.**	**96**
20	**a3** (5)	0.5	r.t.	79
21	**a3** (5)	1	0	18
22	**a3** (5)	1	55	94
23	**a3** (5)	1	80	81
24[e]	**a3** (5)	1	r.t.	40
25[f]	**a3** (5)	1	r.t.	92

[a] General reaction conditions: benzaldehyde (1 mmol), dimedone (2.10 mmol), and water (5 mL) at r.t. [b] Isolated yield. [c] TBAC = tetrabutylammonium chloride. [d] TEAI = tetraethylammonium iodide. [e] Ethanol as the solvent. [f] *N*,*N*-Dimethylformide (DMF) as the solvent.

Table 2 Substrate scope[a]





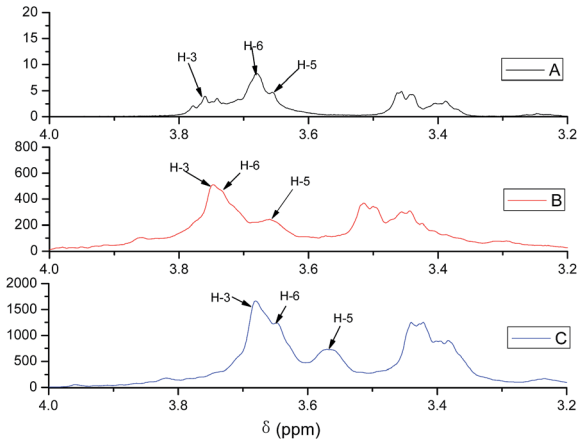
Entry	Aldehyde	1,3-Diketone	Time (h)	Product	Yield[b] (%)	Mp (°C) Obs.	Mp (°C) Lit.
1	C_6H_5CHO (**1a**)	**2a**	1	**3a**	96	205–207	204 (ref. 16)
2	4-Me-C_6H_4CHO (**1b**)	**2a**	1	**3b**	90	135–136	132–133 (ref. 62)
3	3-OH-C_6H_4CHO (**1c**)	**2a**	5	**3c**	95	243	248–250 (ref. 3)
4	4-OH-C_6H_4CHO (**1d**)	**2a**	5	**3d**	91	196–197	187–189 (ref. 59)
5	4-OMe-C_6H_4CHO (**1e**)	**2a**	2	**3e**	93	143	138 (ref. 62)
6	3,4-$(OMe)_2$-C_6H_3CHO (**1f**)	**2a**	2	**3f**	91	183	186–189 (ref. 18)
7	2,5-$(OMe)_2$-C_6H_3CHO (**1g**)	**2a**	2	**3g**	93	154–156	146–148 (ref. 5)
8	3,4,5-$(OMe)_3$-C_6H_2CHO (**1h**)	**2a**	2	**3h**	96	195–196	189–191 (ref. 15)
9	3-OMe-4-OH-C_6H_3CHO (**1i**)	**2a**	2	**3i**	94	206–209	196–197 (ref. 60)
10	4-Cl-C_6H_5CHO (**1j**)	**2a**	2	**3j**	87	147–148	146–148 (ref. 18)
11	4-F-C_6H_4CHO (**1k**)	**2a**	1	**3k**	94	193–195	190–192 (ref. 18)
12	3,4-Cl_2-C_6H_3CHO (**1l**)	**2a**	2	**3l**	85	194	—
13	2-NO_2-C_6H_4CHO (**1m**)	**2a**	1	**3m**	96	191–193	188–190 (ref. 3)
14	3-NO_2-C_6H_4CHO (**1n**)	**2a**	1	**3n**	93	202–205	197–198 (ref. 59)
15	4-NO_2-C_6H_4CHO (**1o**)	**2a**	1	**3o**	95	195	190 (ref. 16)
16	2-Naphthaldehyde (**1p**)	**2a**	1	**3p**	96	218	—
17	3-Pyridinecarboxaldehyde (**1q**)	**2a**	1	**3q**	93	98	—
18	2-Thenaldehyde (**1r**)	**2a**	1	**3r**	92	160–162	156–157 (ref. 61)
19[c]	Terephthalaldehyde (**1s**)	**2a**	5	**3s**	97	322–323	—
20[c]	Isophthalaldehyde (**1t**)	**2a**	5	**3t**	90	303–305	—
21	HCHO (**1u**)	**2a**	1	**3u**	95	188–190	192–193 (ref. 60)
22	CH_3CHO (**1v**)	**2a**	1	**3v**	92	185–186	182–184 (ref. 60)
23	$HCOCO_2Et$ (**1w**)	**2a**	5	**3w**	94	100–101	—
24	Butyraldehyde (**1x**)	**2a**	1	**3x**	97	120–122	130 (ref. 16)
25	Isobutyraldehyde (**1y**)	**2a**	1	**3y**	96	153	153–154 (ref. 3)
26	3-Methyl butanal (**1z**)	**2a**	1	**3z**	94	170–171	—
27	Cyclohexanaldehyde (**1aa**)	**2a**	1	**3aa**	95	185–186	—
28	7-Fluoroisatin (**1bb**)	**2a**	5	**3bb**	58	308	—
29	C_6H_5CHO (**1a**)	**2b**	2	**3cc**	96	213–215	207–208 (ref. 19)
30	C_6H_5CHO (**1a**)	**2c**	2	**3dd**	90	174–175	167–169 (ref. 19)

[a] General reaction conditions: aldehyde (1 mmol), diketone (2.10 mmol), **a3** (0.05 mmol) in water (5 mL) at room temperature. [b] Isolated yields. [c] Dimedone: 4.20 mmol.

to elucidate the host–guest interactions between **a3** and 4-nitrobenzaldehyde. A quasi-molecular ion of 1396.5350 (m/z) was detected, which referred to the dehydration condensation product between **a3** and 4-nitrobenzaldehyde (calcd: m/z = 1396.5360 for $[M + H]^+$) (Fig. 3).

In addition, the inclusion mode of inclusion complexation of **a3**/4-nitrobenzaldehyde was studied by Job's method.[63,64] Within the concentration scope, the Job plot showed a maximum at a molar fraction of 0.5 (Fig. 4), which

Table 3 ^{1}H NMR spectra (500 MHz, in D_2O at 25 °C) of (A) **a3**, (B) **a3**/4-nitrobenzaldehyde complex, and (C) freeze-dried reaction mixture of **a3**/4-nitrobenzaldehyde/dimedone



	δ (ppm)		
Protons	A	B	C
H-3 of **a3**	3.740	3.751	3.683
H-5 of **a3**	3.655	3.659	3.567
H-6 of **a3**	3.681	3.732	3.647

indicated a 1 : 1 inclusion stoichiometry between **a3** and 4-nitrobenzaldehyde.

Thus the inclusion mode of **a3**/4-nitrobenzaldehyde could be demonstrated as patterns of 1 : 1 or 2 : 2 (Fig. 5(A) and (B)).

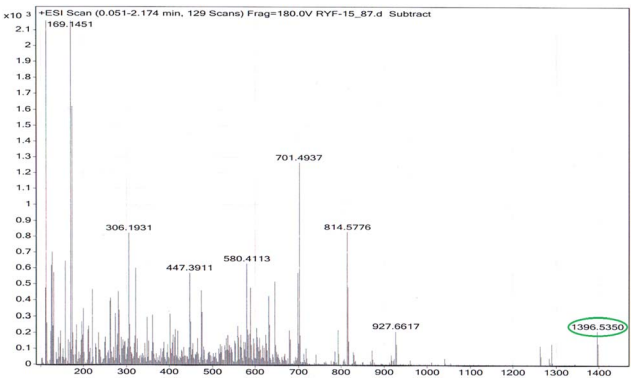


Fig. 3 ESI-MS of **a3**/4-nitrobenzaldehyde complex.

Though more evidences were still needed to verify them, they were surely ascribed to both non-covalent and covalent interactions between the host and guest, which merged supramolecular catalysis and aminocatalysis in this reaction.

Possible reaction mechanism for the **a3**-catalyzed synthesis of tetraketones was proposed based on the above information (Scheme 3). It could be initiated by the formation of iminium intermediate (1) from the dehydration condensation of 4-nitrobenzaldehyde with **a3** inside the cavity of **a3**, followed by the nucleophilic addition of a dimedone. The resultant adduct subsequently underwent a deamination reaction to form the α, β-unsaturated diketone (2) by a H-transfer, towards which a Michael addition was carried out by another dimedone to furnish the tetraketone.

The recycling performance of catalyst **a3** was evaluated with benzaldehyde, dimedone and **a3** in water as a model reaction

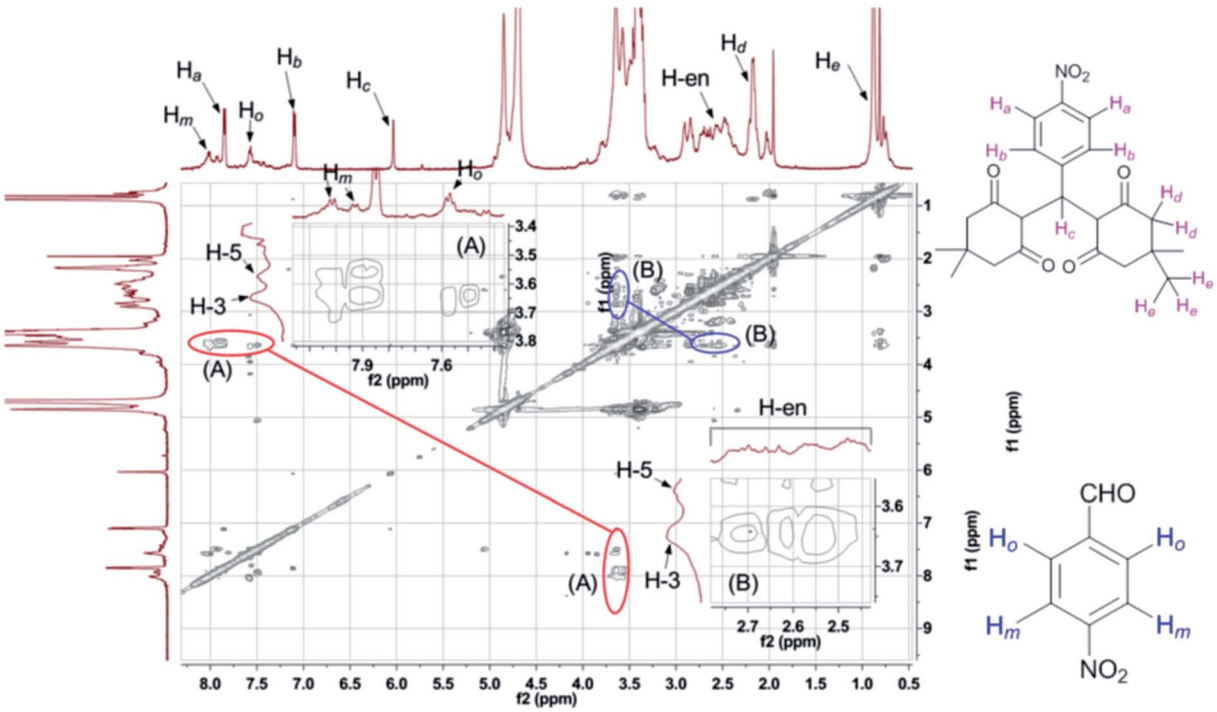


Fig. 2 ROESY of reaction mixture of **a3**/4-nitrobenzaldehyde/dimedone in D_2O at 25 °C.

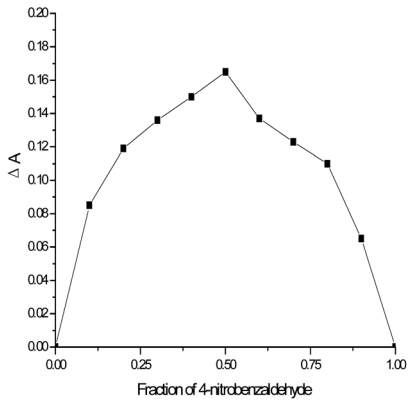


Fig. 4 Job plot for the **a3**/4-nitrobenzaldehyde inclusion system at λ = 267.5 nm ([**a3**] + [4-nitrobenzaldehyde] = 8.0 × 10^{-5} M) in aqueous Na_2CO_3–$NaHCO_3$ buffer (pH = 10.5).

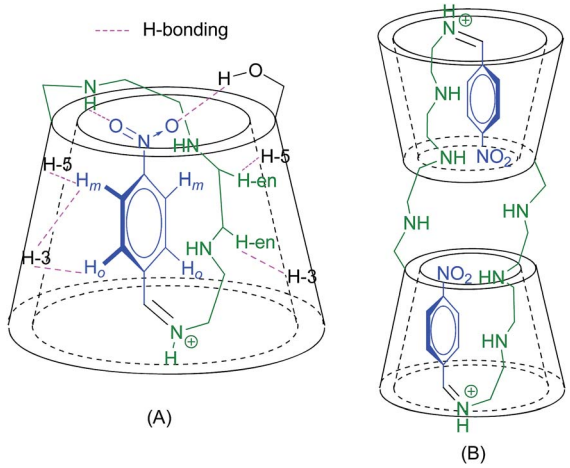


Fig. 5 Possible inclusion mode of **a3**/4-nitrobenzaldehyde.

(Scheme 4). Almost pure product tetraketone could be obtained by filtration after the completion of the reaction, followed by washing the filter cake with water. The filtrate containing catalyst **a3** could be reused directly after removal of tetraketone without any extraction of **a3** from it, without significant loss of yield even after 8 cycles (Fig. 6). Moreover, the catalyst could be easily recovered with a rate up to 84% after 8 cycles from the filtrate by washing with some ethyl acetate followed by evaporation of the aqueous phase *in vacuo*.

Moreover, the synthetic application of this protocol was demonstrated by the gram-scale preparation of xanthendione and acridinedione from tetraketone (Scheme 5). Xanthenedione **4a** could be obtained by refluxing in acetic acid with 89% yield while acridinedione **4b** was synthesized in aqueous ammonium acetate solution with 85% yield.

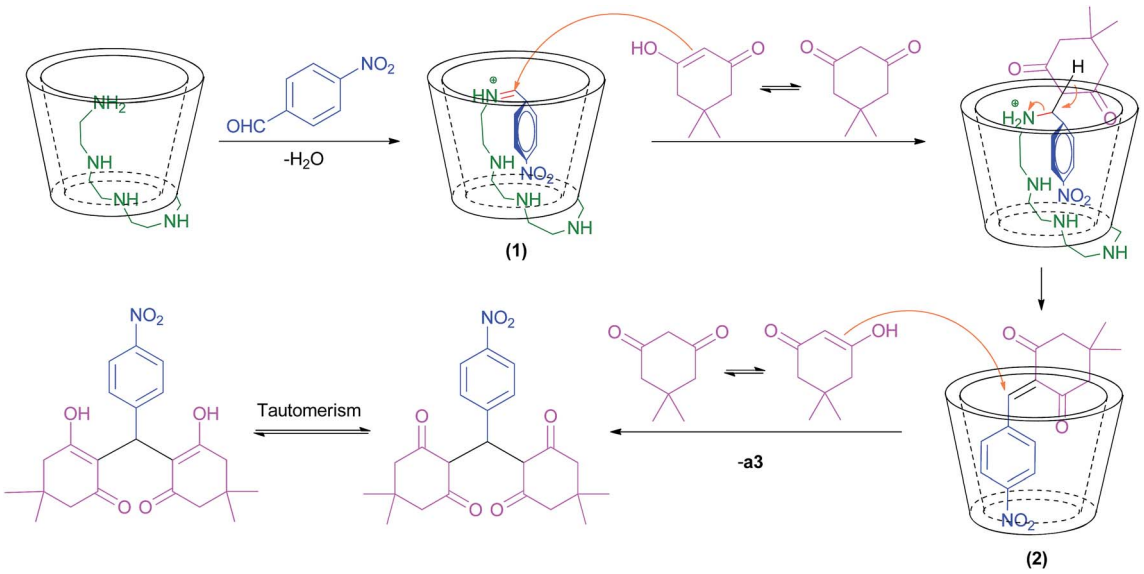
Conclusions

In summary, an efficient one-pot synthesis of tetraketones was established by supramolecular catalysis with amino-appended β-cyclodextrins in water for the first time in this work. Yields of 58–97% could be obtained with up to 30 examples of substrate. The catalyst could be recycled easily without significant loss of efficacy and with high recovery rate after 8 cycles. Moreover, the reaction mechanism was elucidated extensively by spectroscopic analyses, which indicated a catalytic mode of collaboration of supramolecular catalysis and aminocatalysis. This protocol retained excellences of simple operations, environmentally benign conditions, a broad substrate scope, high yields, superb catalyst recycling performance and unique catalytic mechanism.

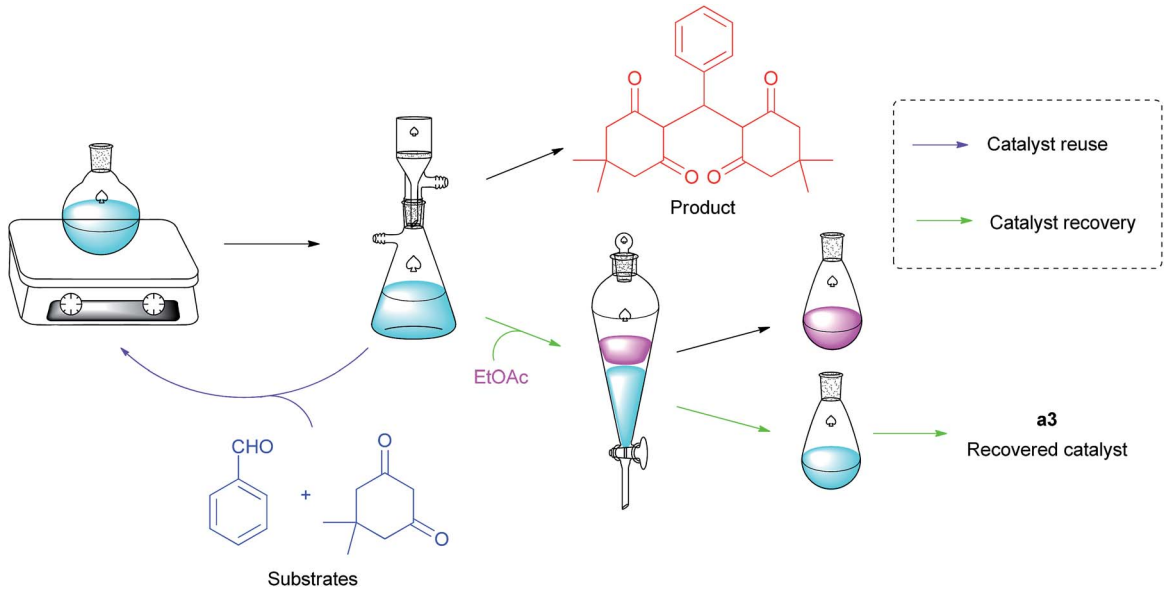
Experimental

General

Melting points (mp, uncorrected) were determined on an RY-1 instrument (Shanghai, China). IR spectra were recorded on



Scheme 3 Possible mechanism for **a3**-catalyzed synthesis of tetraketones.



Scheme 4 Process of catalyst (**a3**) recycling.

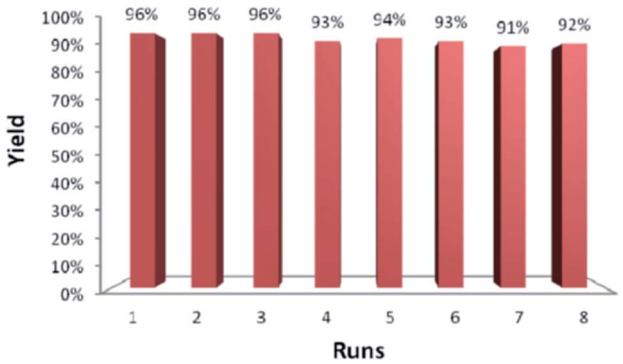
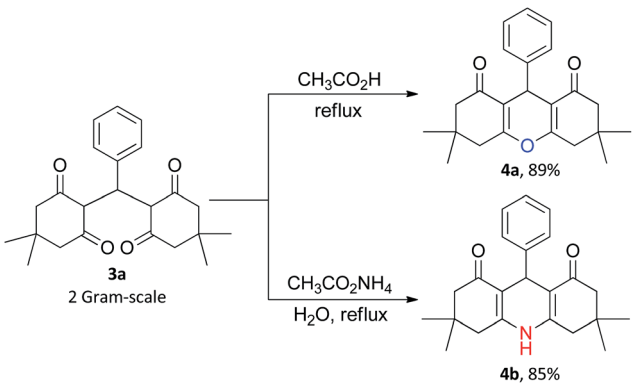


Fig. 6 Yields of catalyst (**a3**) recycling.



Scheme 5 Gram-scale synthetic applications of tetraketone **3a**.

a Bio-Rad FTS-40 FT-IR spectrometer (Bio-Rad, USA). NMR spectra were measured on a Bruker Avance DRX-500 or DRX-400 spectrometer (Bruker, Germany) at 298 K. HRESI-MS data were recorded on a Bruker MicrOTOF Q-II mass spectrometer (Bruker, Germany). Other reagents were all of chemical purity and were used as received.

Typical synthetic procedure of ACDs: synthesis of a3

Mono-6-(4-tolunesulfonyl)-6-deoxy-β-CD (TsCD, 3.0 g) was dissolved with stirring in triethylenediamine (TEA, 20 mL) under nitrogen atmosphere with the evolution of heat the solution (it reached approximately 80 °C) for 12 h. After the completion of reaction, the solution was cooled to room temperature and was added dropwise into acetone (400 mL). White precipitate was collected by suction filtration, which could be further purified by precipitation for 2–3 times (TLC monitored). Pure **a3** was obtained as pale yellow powder (2.5 g, 85%). Mp: 283 °C (decomp.); ^{1}H NMR (400 MHz, D_2O) δ 2.85–2.61 (m, 12H, ethylene of triethylenetetramine), 3.89–3.38 (m, H-2, 3, 4, 5, 6 of CD), 5.08 (s, 7H, H-1 of CD). HRMS (ESI) *m*/*z*: calcd for $C_{48}H_{87}N_4O_{34}$ $[M + H]^+$: 1263.5196, found $[M + H]^+$: 1263.5194.

General procedure for the preparation of tetraketones

Aldehyde (1 mmol) suspended in water (5 mL) was stirred for 1 min, followed by the addition of **a3** (0.05 mol). After stirring constantly for 10 minutes, diketone (2.1 mmol) was added in one portion. After the completion of reaction (monitored by TLC), the resulted mixture was filtered by suction and the filter cake was washed with cool water to obtain a fairly pure product, which could be further purified by recrystallization from ethanol.

Preparation of xanthenedione (4a)

Tetraketone **3a** (2 g, 5.4 mmol) was added into acetic acid (20 mL) and was refluxed for 2 h. The reaction mixture was then evaporated under reduced pressure and was poured into crushed ice. The solid obtained by filtration was crystallized from EtOH–H_2O (8 : 2, v/v) to get pure **4a** (1.69 g, 89%). Mp: 205

°C; IR (KBr, cm^{-1}) 3061, 3031 (=C–H), 2956, 2874 (C–H), 1666 (C=O), 1460 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H, Ar–H), 7.23 (t, J = 7.6 Hz, 2H, Ar–H), 7.11 (t, J = 7.3 Hz, 1H, Ar–H), 4.77 (s, 1H), 2.48 (s, 4H, 2 × CH_2), 2.22 (q, J = 16.3 Hz, 4H, 2 × CH_2), 1.12 (s, 6H, 2 × CH_3), 1.01 (s, 6H, 2 × CH_3); HRMS (ESI) m/z: calcd for $C_{23}H_{26}O_3$ $[M + H]^+$: 351.1960, found $[M + H]^+$: 351.1954.

Preparation of acridinedione (4b)

A mixture of tetraketone **3a** (2 g, 5.4 mmol) and ammonium acetate (1.8 g, 24.0 mmol) in H_2O (20 mL) was refluxed for 6 h. Then the reaction mixture was cooled and was poured into crushed ice. The solid obtained by filtration was purified by recrystallisation from EtOH–H_2O (8 : 2) to yield pure **4b** (1.61 g, 85%). Mp: 279 °C; IR (KBr) cm^{-1} 3283, 3210 (NH), 3064 (=C–H), 2959, 2874 (C–H), 1636 (C=O), 1480 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H, NH), 7.35 (d, J = 7.7 Hz, 2H, Ar–H), 7.20 (t, J = 7.5 Hz, 2H, Ar–H), 7.08 (t, J = 7.3 Hz, 1H), 5.11 (s, 1H), 2.23 (m, 8H, 4 × CH_2), 1.08 (s, 6H, 2 × CH_3), 0.96 (s, 6H, 2 × CH_3); HRMS (ESI) m/z: calcd for $C_{23}H_{27}NO_2$ $[M + Na]^+$: 372.1939, found $[M + Na]^+$: 372.1934.

Preparation of a3/4-nitrobenzaldehyde complex

Catalyst **a3** (0.1 mmol) was added in water (5 mL) and stirred constantly to form a clear solution with the evolution of heat (temperature of solution reached approximately 50 °C). Then a methanol solution of 4-nitrobenzaldehyde (0.1 mmol in 0.3 mL of methanol) was added dropwise followed by cooling to room temperature with stirring. The mixture was subsequently placed at 5 °C for 12 h. It was filtered to remove any insolubles. Dry powder obtained by rotary evaporation of the filtrate could be subjected to spectroscopic analyses.

Recycling of catalyst a3

Aldehyde (1 mmol) suspended in water (5 mL) was stirred for 1 min, followed by the addition of **a3** (0.05 mol). The mixture was stirred constantly for 10 minutes, and then diketone (2.1 mmol) was added in one portion. After the completion of reaction (monitored by TLC), the resultant mixture was filtered by suction and the filter cake was washed with the least amount of water to obtain an almost pure product, which could be further purified by rinsing with more water (about 50 mL) or by recrystallization from ethanol. On the other hand, the next set of substrates was directly added in the previously obtained filtrate containing catalyst **a3** and the mixture was allowed to react to completion. After 8 cycles, the resultant filtrate was washed with ethyl acetate (2 mL) followed by evaporation of the aqueous phase *in vacuo* to retrieve the catalyst **a3** (84%).

Acknowledgements

The authors are grateful to the National Natural Science Foundation of China (21362016) and Analysis & Testing Foundation of Kunming University of Science and Technology (20150714) for financial supports.

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