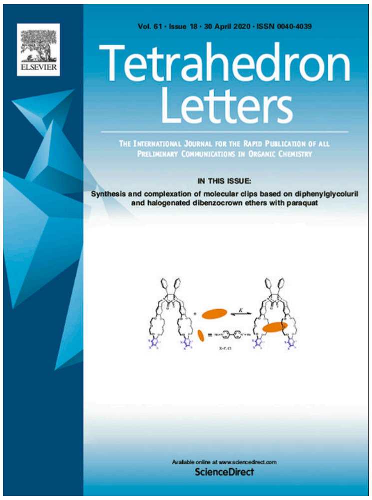


Catalytic efficiency of β-cyclodextrin hydrate-chemoselective reaction of indoles with aldehydes in aqueous medium

Asit Kumar Das, Nayim Sepay, Sneha Nandy, Avishek Ghatak, Sanjay Bhar

PII: S0040-4039(20)30698-5
DOI: https://doi.org/10.1016/j.tetlet.2020.152231
Reference: TETL 152231

To appear in: *Tetrahedron Letters*

Received Date: 6 May 2020
Revised Date: 3 July 2020
Accepted Date: 8 July 2020

Please cite this article as: Das, A.K., Sepay, N., Nandy, S., Ghatak, A., Bhar, S., Catalytic efficiency of β-cyclodextrin hydrate-chemoselective reaction of indoles with aldehydes in aqueous medium, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152231

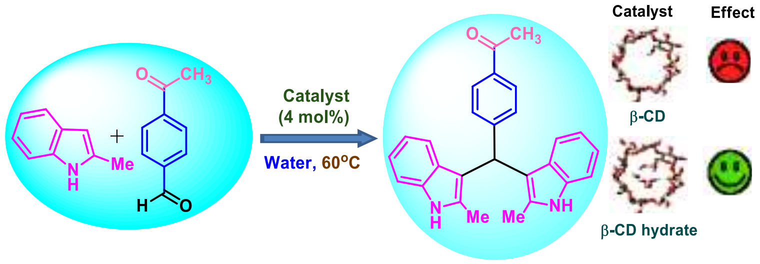
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Catalytic Efficiency of β-cyclodextrin Hydrate-Chemoselective Reaction of Indoles with Aldehydes in Aqueous Medium

Asit Kumar Das,[a] Nayim Sepay,[b] Sneha Nandy,[b] Avishek Ghatak[c] and Sanjay Bhar[b,*]

Leave this area blank for abstract info.



- Atom efficient
- Scalable and sustainable
- C-C bond formation
- Wide tolerance
- Good chemoselectivity
- Recyclable catalyst

Tetrahedron Letters
journal homepage: www.elsevier.com

Catalytic Efficiency of β-cyclodextrin Hydrate-Chemoselective Reaction of Indoles with Aldehydes in Aqueous Medium

Asit Kumar Das,[a] Nayim Sepay,[b] Sneha Nandy,[b] Avishek Ghatak[c] and Sanjay Bhar [b,]*

[a]*Department of Chemistry, Krishnath College, Berhampore, Murshidabad-742101, India*

[b]*Department of Chemistry, Jadavpur University, Kolkata-700032, India*

[c]*Department of Chemistry, Dr. A. P. J. Abdul Kalam Govt. College, New Town, Kolkata- 700156, India*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Aldehydes
Catalysis
Chemoselectivity
Water

ABSTRACT

The catalytic efficiency of β-cyclodextrin hydrate has been investigated towards the eco-compatible synthesis of bis-(indolyl)methanes in aqueous medium by the chemoselective reaction of indoles with differently substituted aryl and alkyl aldehydes under mild reaction conditions. The catalytic attributes of β-cyclodextrin hydrate were also demonstrated through molecular docking and DFT studies. Reactions were slower in D_2O than in H_2O. Aryl and alkyl ketones remained unaffected under the present condition. Excellent chemoselectivity has been established through intermolecular as well as intramolecular competition experiments. Calculation of Green Chemistry Metrices showed high atom economy and small E-factor for the reaction.

Introduction

Cyclodextrins (CDs) are a family of macrocyclic oligosaccharides linked together by α-1,4 glucopyranose subunits and produced enzymatically from starch. β-Cyclodextrin (β-CD) consists of seven D-glucopyranose units forming a cyclic, hollow cone-shaped cavity and possessing hydrophilic exterior due to upper and lower rims decorated with hydroxyl groups as well as hydrophobic internal pocket that embrace substrates selectively[1] through inclusion complexes. But, β-Cyclodextrin hydrate (β-CDH) contains exchangeable hydrogen atoms[2] associated with protonic conductivity which is similar to that of hydrated proteins. The water molecules are present inside and outside of β-CD hydrate (β-CDH) provides an efficient path for the extended movement of protons which is also responsible for the protonic conductivity via a concerted and co-operative translocation of protons through the so-called flip-flop hydrogen bond.[3] The catalytic applications[4] of CDs for the synthesis of biologically important compounds have been reported. But surprisingly the catalytic attributes of β-cyclodextrin hydrate, which behaves differently from β-cyclodextrin, have not been explored much after the maiden report from our group.[5]

Friedel-Crafts reaction is one of the cornerstone reactions for fundamental carbon-carbon (C-C) bond formation and construction of important classes of building blocks.[6] Bis-(indolyl)methanes (BIMs) are prominent and privileged structural motif in bioactive metabolites as well as compounds of both terrestrial and marine origin.[7] A broad range of biologically and pharmacologically active compounds, such as anticancer,[8a] antitumor,[8b] antifungal,[8c] and HIV-1 integrase inhibitor[8d] also carry this structural unit. Therefore, various synthetic strategies such as solid acids,[9a,9b] Lewis acids,[9c,9d,9e,9f] hetero-polyacids,[9g] ionic liquids,[9h,9i] and many others transition metal-free protocols[9j-9q] have been developed during the last few years. Several homogeneous and heretogeneous systems, such as Fe,[10a] Cu,[10b] Zn,[10c] Ag,[10d] Sc,[10e] Mo,[10f] Pd,[10g] Nb,[10h] Ni-Dy complex,[10i] and Dy(OTf)$_3$-ILs,[10j] were also reported for the similar transformations. Even though these reported protocols are satisfactory, but they also suffer from certain disadvantages such as high temperature,[9a,10g] long reaction time,[9p,9q,10c,10g,10i,10j] harsh reaction condition,[10g] use of expensive metal catalysts,[10e-10j] limitation in gram scale production,[9a,10a,10d,10h,10i,10j] insufficient recovery of catalyst,[10b,10d,10e,10g,10i] lack of chemoselectivity,[9a,9h,9m,9n,10a,10d,10f,10j,10k] and involvement of organic solvents[9e,9g,10b,10d,10e,10g,10k] having poor scope to recover and recycle. Therefore, an operationally simple, catalytically efficient, and eco-compatible protocol for the chemoselective synthesis of bis-(indolyl)methanes through the three component reaction[11] involving indoles[12] is of great demand from the standpoint of sustainability. The use of β-cyclodextrin hydrate (β-CD hydrate) as a mildly acidic, efficient and recyclable catalyst during an organic reaction in aqueous medium has been reported[5] for the first time from our group. In continuation of our investigations in this direction we report herein the synthesis of bis-(indolyl)methanes using β-CD hydrate as an eco-friendly catalyst through chemoselective Friedel-Crafts alkylation of substituted indoles with differently substituted aromatic and aliphatic aldehydes in aqueous medium where the assistive role of water molecules present inside the cavity of β-CD hydrate was established.

Results and Discussion:

We initiated our experiments by investigating the Friedel-Crafts alkylation reaction between 2-methylindole **1a** (1 mmol) with 4-methoxybenzaldehyde **2a** (0.5 mmol) in water at 60°C in the presence of different catalysts with the variation of reaction

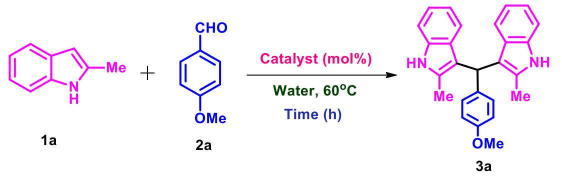
---

* Corresponding author. Tel.: +918697179547; fax: +91-33-24137902; e-mail: sanjay.bhar@jadavpuruniversity.in

tin

(indolyl)methanes **3a** (Table 1).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Mole (%)	Time (h)	Yield of 3a (%)[b]
1	- -	- -	10	- -
2	β-CD	2	3	52
3	β-CD	6	6	61
4	β-CD	8	6	68
5	β-CD hydrate	2[c]	6	80
6	β-CD hydrate	4[c]	3	92
7	β-CD hydrate	6[c]	5	92
8	β-CD hydrate	8[c]	3	93
9	α- CD	10	10	25
10	γ-CD	10	10	20
11	18-crown-6	6	8	Trace
12	Starch	6	8	--

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), catalyst (as indicated), water (3mL) at 60ºC. [b]Isolated yield. [c]Based on the molecular formula $C_{42}H_{70}O_{35}·11H_2O$ [13]

As shown in Table 1, the reaction did not occur at all in the absence of any catalyst (Entry 1), the unreacted substrates were isolated intact. The reaction was less responsive in presence α-CD (Entry 9), γ-CD (Entry 10) and 18-crown-6 (Entry 11). With β-CD, **3a** was obtained with moderate yield (entries 2-4). Surprisingly, when β-CD hydrate was used as a catalyst in lesser amount (2 mol %) the yield of the reaction was significantly increased to 80% (entry 5) but no reaction took place in the absence of β-CD hydrate even at higher temperature (80°C). Therefore, the necessity, efficacy and applicability of β-CD hydrate for this organic transformation were firmly established. Looking for an improvement in yield, the amount of catalyst was increased. Best result was obtained using 4 mol % of β-CD hydrate where the yield was increased to 92% in lesser time (entry 6). Excess catalyst beyond this proportion (4 mol %) did not afford to better substrate conversion and increment of the yield (entries 7, 8). Hence the optimized condition for further studies has been chosen according to entry 6. Using starch as the catalyst in place of β-cyclodextrin hydrate, the reaction did not occur at all and the unreacted substrates were isolated intact (entry 12). The greater catalytic efficacy of β-CD hydrate in the present metal-free reaction in aqueous medium (entries 5-8) compared to β-CD (entries 2-4) is at par with our previous experience.[5] To further establish the efficacy of β-CD hydrate, we next carried out a comparative study between β-CD and β-CD hydrate using **1a** (1 mmol) and **2a** (0.5 mmol) in presence of H_2O and D_2O at 60ºC (Table 2).

Table 2 Comparative study between β-CD and β-CD hydrate[a]

Entry	Catalyst	Solvent (3 mL)	Mole (%)	Time (h)	Conversion(%)[b]
1	β-CD	H_2O	4	3	67
2	β-CD	D_2O	4	3	28
3	β-CD hydrate	H_2O	4	3	100
4	β-CD hydrate	D_2O	4	3	62

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), temperature 60ºC. [b]Measured by ^{1}H NMR.

ence of β-CD hydrate in H_2O as well as in D_2O compared to β-CD. Furthermore, the progress of the reaction was monitored at different time intervals using β-CD and β-CD hydrate separately as catalyst under the optimized reaction condition using H_2O as well as D_2O as the reaction medium (Figure 1). It was evident from Figure 1 that the reactions in H_2O were faster than in D_2O and better conversion was achieved in the former case. Hence, the isotope effect rendered by the reaction medium has been observed. The extent of conversion using β-CD as catalyst in H_2O was moderate. Hence the essentiality of water molecules inside the cavity of β-CD hydrate was conclusively proved.

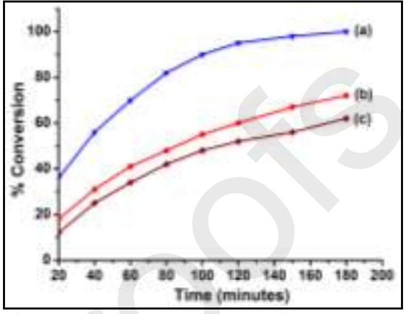


Figure 1 Plot of the percentage conversion of **3a** with time using **1a** (1.0 mmol), **2a** (0.5 mmol) and catalyst (4 mol %) at 60^{0}C in solvent (3 mL); (a) β-CD hydrate in H_2O; (b) β-CD in H_2O; (c) β-CD hydrate in D_2O.

β- CD hydrate bears negligible toxicity as evident from its MSDS.[14] This is sparingly soluble in water under ambient condition but becomes completely miscible in aqueous reaction medium at the reaction temperature (60°C). Thus it offers the advantages of homogeneous catalysts during the reaction as well as the benefits of heterogeneous catalysts during isolation of the products and separation of the catalyst. After the completion of the reaction, the reaction mixture was cooled in ice-water and crude product was dissolved in ethyl acetate. The precipitated catalyst was separated by filtration, washed with ethyl acetate, dried and reused directly in a fresh reaction with a little variation of yield (Figure 2). The reactions took place in aqueous condition and did not require inert environment and any organic co-solvent as the reaction medium. It utilizes ethyl acetate as an eco-friendly solvent for the isolation of the product. Moreover, the reactions are highly atom-efficient and generate water as the sole and innocuous side-product. Therefore, this novel β-CD hydrate catalyzed metal-free Friedel-Crafts alkylation reaction in aqueous medium seems to be eco-compatible in terms of reaction medium, operational simplicity, and recyclability of catalysts and solvents of insignificant toxicity. The green metrics calculated for the optimized reaction (between **1a** and **2a**) show high atom economy and small E-factor (See the Supplementary Materials). So this metal-free catalytic protocol in aqueous medium is proved to be highly sustainable from the standpoints of efficacy, less toxicity, economical viability, recyclability of the catalyst as well as minimized waste formation.

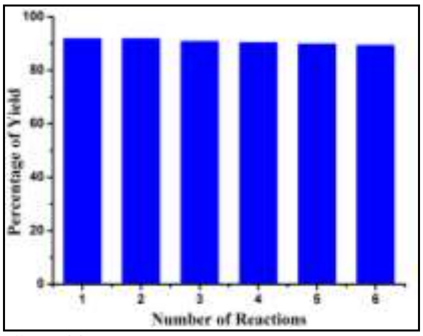


Figure 2 Recycling of β-CD hydrate using **1a** (1.0 mmol), **2a** (0.5 mmol) and β–CD hydrate (4 mol %) as catalyst at 60^{0}C for 3 hours in water (3 mL); % of yield was the isolated yield of **3a**.

The molecular docking study (Figure 3) revealed that the presence of water molecules inside the cavity of β-CD hydrate (β-CDH) might facilitate the inclusion of the benzaldehyde more effe different interaction of benzaldehyde with β-CDH and β-CD with a preferred orientation of the ligands inside the cavity. The docked pose of benzaldehyde was more included within the cavity of β-CDH than β-CD. The –CHO group of benzaldehyde formed one hydrogen bond (1.78 Å) with the water molecules present within the cavity of β-CDH (Figure 3b) whereas the same formed two hydrogen bonds (2.17 Å and 2.86 Å) with the -CH_2OH group of β-CD located near the wider side (secondary hydroxy rim) (Figure 3a). However, the binding modes of 2-methylindole with β-CD and β-CDH seem to be nearly similar (Figures 3c and 3d). The hydrogen bonding interaction of benzaldehyde with the water molecules inside the β-CDH cavity (which are also believed to possess more protic behavior due to flip-flop movement) might increase the electrophilicity of the formyl carbon; therefore the nucleophilic attack of 2-methylindole on benzaldehyde seems to be facilitated. The docked pose of corresponding bis-(indolyl)methane was more excluded through one hydrogen bonding interaction (2.86 Å) in the β-CDH whereas it was slightly included inside the cavity of β-CD (Figures 3e and 3f).

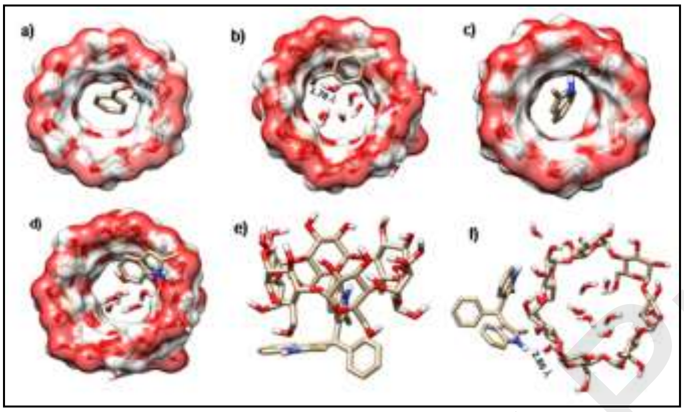


Figure 3 Docking poses showing the interaction sites of a) benzaldehyde with β-CD, b) benzaldehyde with β-CD hydrate, c) 2-methylindole with β-CD, d) 2-methylindole with β-CD hydrate, e) bis-(indolyl)methane with β-CD, f) bis-(indolyl)methane with β-CD hydrate.

We tried to get a deeper insight about the beneficiary effect of water molecules present inside the cavity of β-CD hydrate towards this aqueous reaction using density functional theory (DFT). The structures of 2-methylindole as well as benzaldehyde with hydrogen bonded water at a distance of 1.78 Å (Figure 3b) and without hydrogen bonding (Figure 3a) were optimized (Figure 4). The result shows that the hydrogen bonding between carbonyl oxygen and water increases the positive Mulliken charge on the carbonyl carbon (Figure 4a, ii). Thus, due to hydrogen bonding with the water molecule inside the cavity of β-CD hydrate, the electrophilicity of carbonyl carbon of benzaldehyde is increased accompanied with the greater stabilization of its HOMO and LUMO (Figure 4b). Under hydrogen bonded condition, HOMO and LUMO of benzaldehyde are stabilized by 0.24 eV and 0.29 eV respectively (Figure 4b). Therefore, the nucleophilic attack by 2-methylindole through its high energy HOMO to the low energy LUMO of hydrogen bonded benzaldehyde is more facilitated with respect to benzaldehyde devoid of hydrogen bonding (Figure 4b**,** shown with the dotted line). Calculations also indicate that the orbital coefficients of frontier molecular orbitals are enhanced due to hydrogen bonding on the carbonyl carbon atom of (ii) over (i) and its LUMO of same symmetry with the HOMO of C_2-C_3 bond in 2-methylindole (Figure 4b). These observed results provide a supportive rationale towards the better catalytic attributes of β-CD hydrate compared to β-CD for the present reaction.

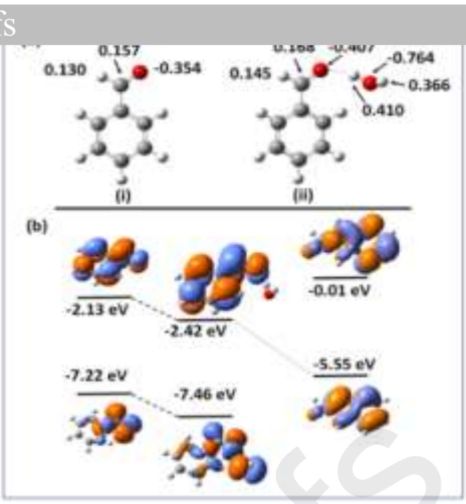
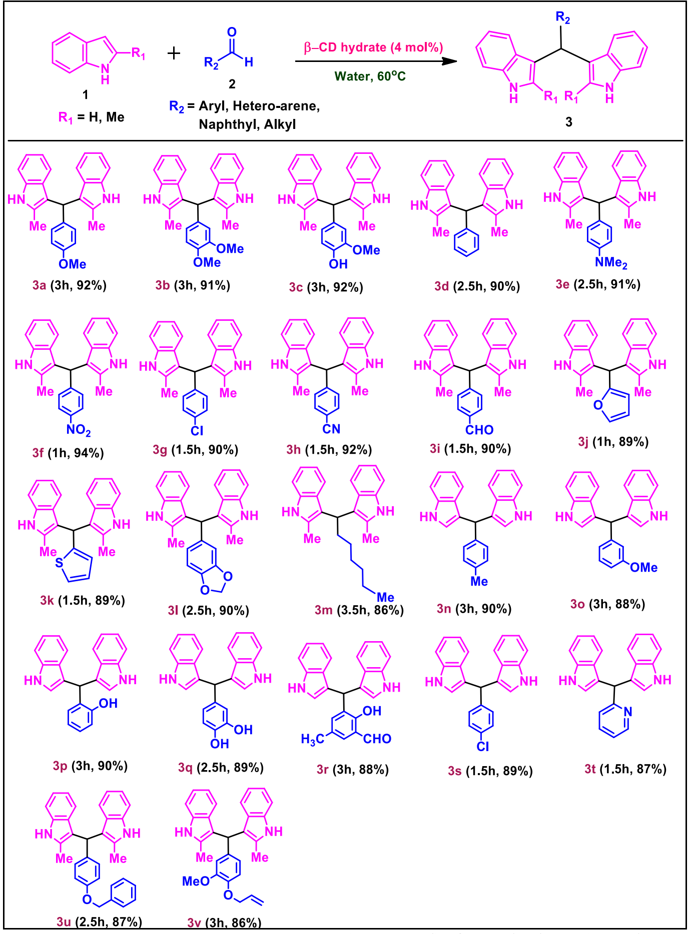


Figure 4 (a) Optimized structures of benzaldehyde with and without hydrogen bonded water and (b) The frontier orbital energy level of HOMO and LUMO of 2-methylindole and benzaldehyde with as well as without hydrogen bonded water.

In order to explore the scope and limitations of this meal-free eco-friendly protocol, indoles **1** were reacted with structurally varied aldehydes **2** in aqueous medium in the presence of β-CD hydrate as a catalyst (Table 3). As evident from Table 3, 2-methylindole (**1a**) reacted efficiently with the benzaldehyde as well as other aryl aldehydes bearing electron donating substituents (**2a-2e**) and electron withdrawing substituents (**2f-2i**) to give the corresponding bis-indolylmethanes with excellent yield (**3a-3i**). Reaction between **1a** and less electrophilic aromatic aldehyde (**2e**) under the optimized condition is known as the Ehrlich test.[15]

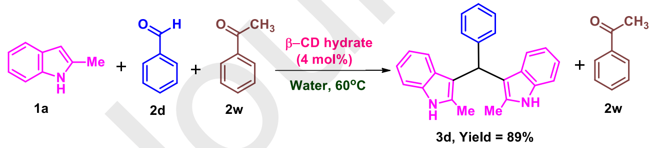
Table 3 β-CD hydrate catalysed reactions of indoles with aldehydes



Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), β CD hydrate (4 mol%), water (3 mL) at 60°C for indicated time.

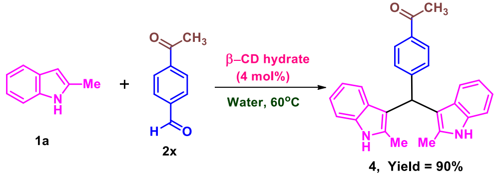
Si to participate in the same protocol to yield the corresponding products (**3n-3s**). Phenolic-OH groups remained unaffected during this reaction and the reaction was very facile even with the –OH group at the *ortho*-position (**3p-3r)**. Acid-sensitive heteroaryl moieties also survived during this reaction which paved the way towards the efficient construction of important molecular skeletons densely loaded with heterocycles (**3j**, **3k** and **3t**) in good yields. Hydrolysable group like methylenedioxy also remained unaffected in the aqueous reaction medium to produce **3l** in good yield. It is extremely important to note the remarkable survival of another acid-sensitive hydrolysable functional group –CN in this aqueous protocol, where the corresponding product **3h** was obtained with 92% yield. The survival of -CN was confirmed by the signal at δ119.4 (specific for –CN) in the ^{13}C-NMR spectrum of **3h**. With terephthaldehyde (**2i**), the bis-(indolyl)methane (**3i**) was obtained in high yield (90%) where one –CHO participated in the reaction and the other –CHO remained unaffected in spite of using higher concentration of **1a**. A sharp singlet at δ9.96 in ^{1}H NMR spectrum as well as a signal at δ197.0 in ^{13}C NMR spectrum confirmed the presence of one formyl group in **3i**. Such a regioselectivity was also observed in **3r.** This is an extremely important attribute of the present protocol in contrast to many reported methods where no such regioselectivity was observed.[10d,e] Aliphatic aldehyde (**2m**) also reacted quite efficiently in the present protocol with **1a** to produce **3m** in 86% yield. Highly vulnerable groups like O-benzyl and O-allyl were also tolerated under the optimized reaction condition to furnish the products **3u** and **3v** in 87% and 86% yields respectively. The bis-(indolyl)methane (**3q**), obtained in 89% yield through the reaction between 3,4-dihydroxybenzaldehyde and **1b**, has been reported to exhibit excellent biological activity such as HIV-1 integrase inhibition.[9e]

Interestingly, aryl alkyl ketone, diaryl ketone and dialkyl ketone (acetophenone, benzophenone and 2-butanone respectively) as well as ester (methyl benzoate) did not react with indole under this β-CD hydrate catalyzed aqueous protocol where the substrates were recovered totally unaffected. Encouraged by the above observations, we ventured to investigate the chemoselectivity of our newly developed aqueous protocol. Intermolecular competition reaction was carried out with a mixture of 2-methylindole (**1a**), benzaldehyde (**2d**) and acetophenone (**2w**) under the optimised reaction condition which produced **3d** (derived from benzaldehyde) exclusively and acetophenone (**2w**) was recovered totally unaffected (Scheme 1).



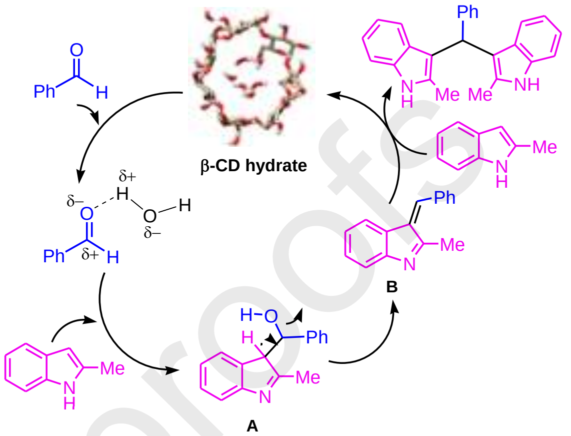
Scheme 1 Intermolecular competition experiment to demonstrate chemoselectivity.

The aforesaid protocol was further applied to the intramolecular competition experiment with 4-acetylbenzaldehyde (**2x**) where only the formyl group reacted selectively with **1a** leading to the product **4** exclusively with 90% yield leaving the ketomethyl moiety totally intact (Scheme 2). This is a vital and additional attribute of the said protocol in contrast to many of the earlier reports[9a,9h,9m,9n,10a,10d,10f,10j,10k] where no such chemoselectivity was observed.



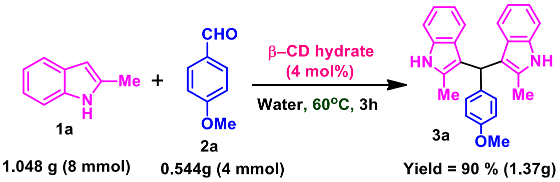
Scheme 2 Intramolecular competition experiment to demonstrate chemoselectivity.

yzed aqueous reaction is depicted in Scheme 3. Based on the aforsaid investigations (Figures 3b and 4a, ii), it is presumed that nucleophilic attack from higher energy HOMO of 2-methylindole to lower energy LUMO of benzaldehyde (due to its hydrogen bonding with the water molecules inside the cavity of β-CD hydrate) is enhanced and the intermediate (A) was rapidly formed in the first step. Subsequent dehydration of the intermediate (A) forms the corresponding 3-arylidene-3*H*-indole (B), which on further nucleophilic attack by another 2-methylindole affords the product.



Scheme 3 Plausible mechanism for the synthesis of bis-(indol-3-yl)-methane catalysed by β-CD hydrate.

To demonstrate the practical utility and scalability of our newly developed protocol, a gram scale reaction between **1a** and **2a** was carried out (Scheme 4). The reaction mixture was extracted with EtOAc and the crude product **3a** was further purified by filtration chromatography on a short column of silica gel using ethyl acetate-hexane as eluent.



Scheme 4 Gram-scale applicability of β-CD hydrate catalysed protocol.

The comparison of our present metal-free protocol with some of the earlier reports is summarized in Table 4.

Table 4 Comparison of the catalytic efficiency of various catalyst reported in the literature for the synthesis of 3,3'-(p-tolylmethylene)bis(1H-indole)

Entry	Catalyst	Solvent	Time (h), Temp(°C)	Yield (%)	Ref.
1	--	Ethyl lactate: H_2O	0.5h, U.S., RT	91	9n
2	[DABCO-H][HSO_4]	--	2h, 90°C	79	9o
3	α-chymotrypsin	H_2O	24h, 70°C	90	9p
4	Lipase enzyme	H_2O	36h, 55°C	95	9q
5	ZnO-RGO	EtOH:H_2O	12h, RT	86	10c
6	TPPMS/CBr_4	CH_3CN	4h, RT	72	10k
7	β-CD hydrate	H_2O	3h, 60°C	89	**This work**

Some of the studies listed in Table 4 (entries 1-6) involved the use of costly catalyst,[9p,9q,10c,10k] multistep synthesis of catalyst,[9o,10c,10k] long reaction time,[9p,9q,10c] lack of chemoselectivity,[9n,10k] and the tedious product isolation procedure[9o] for the synthesis of BIMs. The present β-cyclodextrin hydrate-catalyzed metal-free protocol in aqueous medium mostly does away with these shortcomings (entry 7). Therefore, the present protocol seems to have enough potential to be a better, economically viable, ecocom

wider applicability compared to many of the earlier methods reported for the construction of bis-(indolyl)methane framework.

Conclusion

Catalytic efficiency of β-cyclodextrin hydrate has been investigated towards the synthesis of bis-(indol-3-yl)-methanes through the Friedel-Crafts alkylation reaction of indoles with aryl, heteroaryl as well as alkyl aldehydes under mild reaction condition. This newly developed atom-economical protocol shows good chemoselectivity which has been substantiated through intermolecular as well as intramolecular competition experiments. Practical synthetic utility was also demonstrated by gram scale applicability. The salient features of the present method are procedural simplicity, excellent chemoselectivity, tolerance of various sensitive moieties during the reaction, wide substrate scope as well as eco-compatibility in terms of using water as the most innocuous reaction medium, the ready accessibility and recyclability of the catalyst of lower toxicity compared to most of the existing ones and minimization of waste formation owing to high atom economy and small E-factor.

Acknowledgments

Financial assistance from RUSA 2-Programme and UGC-CAS-II programme in Chemistry at Jadavpur University are gratefully acknowledged. S. N. Thanks DST, INSPIRE, New Delhi for senior research fellowship. Thanks to Mr. N. Dutta of IACS and Mr. R. Biswas of JU for necessary assistance.

References and notes

1. Wang, Q.; Chen, Y.; Liu, Y. *Polym, Chem-UK,* **2013**, *4*, 4192.
2. Usha, M. G.; Wittebort, R. J. *J. Mol. Biol.* **1989**, *208*, 669-678.
3. Anagnostopoulou, A.; Apekis, L.; Tsoukaris, G. *IEEE Trans. Electrical Insulation*, **1992**, *27*, 801.
4. (a) Madhav, B.; Murthy, S. N.; Kumar, B. A.; Ramesh, K.; Nageswar, Y. V. D.; *Tetrahedron Lett.* **2012**, *53*, 3835-3838; (b) Noel, S.; Leger, B.; Ponchel, A.; Philippot, K.; Nowicki, A. D.; Roucoux, A.; Monflier, E. *Catal. Today.* **2014**, *235*, 20-32; (c) Hapiot, F.; Bricout, H.; Menuel, S.; Tilloy, S.; Monflier, E. *Catal. Sci. Technol.* **2014**, *4*, 1899-1908; (d) Kumar, A.; Shukla, R. D. *Green Chem.* **2015**, *17*, 848-851; (e) Shinde, V. V.; Jeong, D.; Joo, S. W.; Cho, E.; Jung, S. *Catal. Commun.* **2018**, *103*, 83-87.
5. Ghatak, A.; Khan, S.; Bhar, S. *Adv. Synth. Catal.* **2016**, *358*, 435-443.
6. (a) Friedel, C.; Crafts, J. M. *J. Chem. Soc.* **1877**, *32*, 725-791; (b) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485-1487; (c) Ottoni, O.; Neder, A. D. V. F.; Dias, A. K. B.; Ruz, R. P. A. C; Aquino, L. B. *Org. Lett.* **2001**, *3*, 1005-1007; (d) Wynne, J. H.; Stalick, W. M. *J. Org. Chem.* **2002**, *67*, 5850-5853; (e) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *44*, 238-242; (f) Jia, Y. X.; Xie, J. H.; Duan, H. F.; Wang, L. X.; Lin Zhou, Q. *Org. Lett.* **2006**, *8*, 1621-1624; (g) Wang, Y. Q.; Song, J.; Hong, R.; Hongming, Li.; Li Deng. *J. Am. Chem. Soc.* **2006**, *128*, 8156-8157; (h) Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501-1507; (i) Downey, C. W.; Poff, C. D.; Nizinski, A. N. *J. Org. Chem.* **2015**, *20*, 10364-10369; (j) Deng, X. F.; Wang, Y. W.; Zhang, S.; Li, L.; Li, G. X.; Zhao, G.; Tang, Z. *Chem. Commun.*, **2020**, *56*, 2499-2502.
7. Garbe, T. R.; Kobayashi, M.; Shimizu, N. *J. Nat. Prod.* **2000**, *63*, 596-598.
8. (a) Grosso, C.; Cardoso, A. L.; Lemos, A.; Varela, J.; Rodrigues, M. J.; Custodio, L.; Barreira, L.; Melo, T. *Eur. J. Med. Chem.* **2015**, *93*, 9-15; (b) Li, D.; Wu, T.; Liang, K.; Xia, C. *Org. Lett.*
, J. A.; Scott, S. L.; Barta, K.; Ford, P. C. *Catal. Sci. Technol.* **2016**, *6*, 2984-2994; (d) Srivastava, A.; Agarwal, A.; Gupta, S. K.; Jain, N. *RSC Adv.* **2016**, *6*, 23008-23011.
9. (a) Mendes, S. R.; Thurow, S.; Fortes, M. P.; Penteado, F.; Lenardao, E. J.; Alves, D.; Perin, G.; Jacob, R. G. *Tetrahedron Lett.* **2012**, *53*, 5402-5406; (b) Esmaielpour, M.; Akhlaghinia, B.; Jahanshahi, R. *J. Chem. Sci.* **2017**, *129*, 313-328; (c) Shaikh, K. A.; Mohammed, Z. A.; Patel, N. T.; Syed, S. A.; Patil, V. A. *Res. J. Pharm. Biol. Chem. Sci.* **2010**, *1*, 730-736; (d) Sadaphal, S. A.; Shelke, K. F.; Sonar, S. S.; Madje, B. R.; Shingare, M. S. *Bulletin of the Catalysis Scoeity of India,* **2008**, *7*, 111-114; (e) Swetha, A.; Babu, B. M.; Meshram, H. M. *Tetrahedron Lett.* **2015**, *56*, 1775-1779; (f) Wu, Z.; Wang, G.; Yuan, S.; Wu, D.; Liu, W.; Ma, B.; Bi, S.; Zhan, H.; Chen, X. *Green Chem.* **2019**, *21*, 3542-3546; (g) Selvakumar, K.; Shanmugaprabha, T.; Annapoorani, R. *Synth. Commun.* **2017**, *47*, 913-927; (h) Tran, P. H.; Nguyen, X. T. T.; Chau, D. K. N. *Asian J. Org. Chem.* **2018**, *7*, 232-239; (i) Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Shakouri, M.; Otokesh, S.; Ekrami, T.; Doosti, R. J. *Iran. Chem. Soc.* **2007**, *4*, 393-401; (j) Vaghei, R. G.; Veisi, H. *J. Braz. Chem. Soc.* **2010**, *21*, 193-201; (k) Sujatha, K.; Perumal, P. T.; Muralidharan, D.; Rajendaran, M. *Indian. J. Chem.* **2009**, *48(B)*, 267-272; (l) Hasaninejad, A.; Mohammadizadeh, M.R.; Babamiri, S. F. *2nd International IUPAC Conference on Green Chemistry, Russia,* **2008**; 14-19; (m) Patil, V. D.; Dere, G. B.; Rege, P. A.; Patil, J. J. *Syn. Commun.*, **2011**, *41*, 736-747; (n) Gao, G.; Han, Y.; Zhang, Z. H. *ChemistrySelect.* **2017**, *2*, 11561-11564; (o) Xu, D. Z.; Tong, J.; Yang, C. *Synthesis*, **2016**, *48*, 3559-3566; (p) Sun, D.; Jiang, G.; Xie, Z.; Le, Z. *Chin. J. Chem.* **2015**, *33*, 409-412; (q) Fu, Y.; Lu, Z.; Fang, K.; He, X.; Xu, H.; Hu, Y. *RSC Adv.*, **2020**, *10*, 10848-10853.
10. (a) Li, D.; Wang, J.; Chen, F.; Jing, H. *RSC Adv.* **2017**, *7*, 4237-4242; (b) Kothandapani, J.; Ganesan, A.; Vairaprakash, P.; Ganesan, S. S. *Tetrahedron Lett.* **2015**, *56*, 2238-2242; (c) Bahuguna, A.; Kumar, S.; Krishnan, V. *ChemistrySelect.* **2018**, *3*, 314-320; (d) Beltra, J.; Gimeno, M. C.; Herrera, R. P. *Beilstein J. Org. Chem.* **2014**, *10*, 2206-2214; (e) Mohapatra, S. S.; Wilson, Z. E.; Roy, S.; Ley, S. V. *Tetrahedron*, **2017**, *73*, 1812-1819; (f) Bahuguna, A.; Kumar, S.; Sharma, V.; Reddy, K. L.; Bhattacharyya, K.; Ravikumar, P. C.; Krishnan, V. *ACS Sustainable Chem. Eng.* **2017**, *5*, 8551-8567; (g) Guo, S.; Fang, Z.; Zhou, B.; Hua, J.; Dai, Z.; Yang, Z.; Liu, C.; He, W.; Guo, K. *Org. Chem. Front.* **2019**, *6*, 627-631; (h) Mendes, S. R.; Thurow, S.; Penteado, F.; Silva, M. S. da.; Gariani, R. A.; Perin, G.; Lenardao, E. J. *Green Chem.* **2015**, *17*, 4334-4339; (i) Gorantla, N. S.; Reddy, P. G.; Abdul Shakoor, S. M.; Mandal, R.; Roy, S.; Mondal, K. C. *ChemistrySelect.* **2019**, *4*, 7722-7727; (j) Xueling, M.; Sanzhong, L.; Jiaqi, H.; Cheng, J. P.; *Tetrahedron Lett.* **2004**, *45*, 4567-4570; (k) Huo, C.; Sun, C.; Wang, C.; Jia, X.; Chang, W. *ACS Sustainable Chem. Eng.* **2013**, *1*, 549-553.
11. (a) Rajeswaran, W. G.; Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1999**, *64*, 1369-1371; (b) Yadav, J. S.; Subba Reddy, B. V.; Yadav, N. N.; Gupta, M. K. *Tetrahedron Lett.* **2008**, *49*, 2815-2819; (c) Srihari, P.; Singh, V. K.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *50*, 3763-3766.
12. Fukuyama, T.; Chen, X.; Ge Peng. *J. Am. Chem. Soc.* **1994**, *116*, 3127-3128.
13. (a) Usha, M. G.; Wittebort, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 1541-1548; (b) Sabadini, E.; Cosgrove, T.; Egidio, F. C. *Carbohydr. Res.* **2006**, *341*, 270-274.
14. https://www.nwmissouri.edu/naturalsciences/sds/b/Beta-Cyclodextrin%20hydrate.pdf
15. (a) Ehrlich, P. *Med. Woche*. **1901**, 151; (b) Seyedeh, F. H.; Toktam, Z.; Zahra, N. *Bull. Korean Chem. Soc.* **2013**, *34*, 117.

Supplementary Material General experimental procedure and the characterization data of the final compounds are available as supporting information.

HIGHLIGHTS

Catalytic Efficiency of β-cyclodextrin Hydrate-Chemoselective Reaction of Indoles with Aldehydes in Aqueous Medium

Asit Kumar Das, Nayim Sepay, Sneha Nandy,
Avishek Ghatak and Sanjay Bhar *

- Metal-free aqueous phase catalysis with high atom economy
- Tolerance of various sensitive moieties under eco-compatible condition
- Recyclable, stable and sustainable catalytic system
- Excellent chemoselectivity as well as gram scale applicability
- Generation of water as the sole and innocuous side-product

STATEMENT

Name of the Journal where submitted:
Tetrahedron Letters

Title of the paper: Catalytic Efficiency of β-cyclodextrin Hydrate-Chemoselective Reaction of Indoles with Aldehydes in Aqueous Medium

Authors: Asit Kumar Das, Nayim Sepay, Sneha Nandy, Avishek Ghatak and Sanjay Bhar*

“This is to declare that there is no conflict of interest in this article.”

Sanjay Bhar

Corresponding author

Department of Chemistry, Jadavpur University, India