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β-Cyclodextrin Catalysed C-C Bond Formation *via* C(sp^3)-H Functionalization of 2-Methyl azaarenes with Diones in aqueous medium

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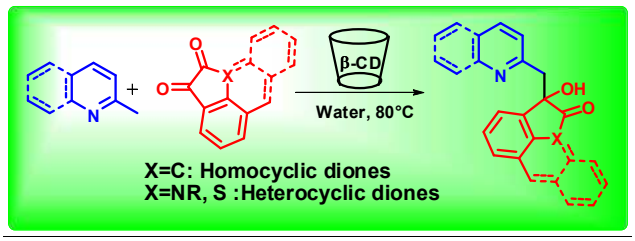
ABSTRACT: First β-cyclodextrin catalysed C(sp3)-H functionalization of 2-alkyl-azaarenes with homocyclic as well as heterocyclic diones in water has been developed. This bio-mimetic catalyst oriented methodology provides a sustainable and green protocol for C-H functionalization, the area mainly dominated by transition metals.

In twenty first century the development of new methods for C–H functionalization and their applications has been one of the most blossomed areas of research.[1-2] C-H bond functionalization is considered as powerful and shortest approach[3] for construction of carbon–carbon and carbon-heteroatom bonds, which have potential application in the synthesis of biologically relevant molecules. 2-Alkyl azaarenes such as 2-methyl pyridine and 2-methyl quinoline are ubiquitous structural motifs in biologically compatible molecules and act as valuable precursors for a wide range of 2-alkyl heterocycles.[4] Forasmuch, digits of attempts have been presumed to the functionalization of 2-methyl-azaarenes. Recently, numerous catalysts and procedures have been reported for direct C(sp3)–H bond functionalization of 2-alkyl-substituted azaarenes.[5-9] Keeping in account the utility of C–H bond functionalization, in the scenario of green chemistry, the search of more economical, environmentally benign catalyst and medium is yet desirable.

From the standpoint of green chemistry water is known to be a potential replacement for organic solvents[10-14] which is readily available, cost effective, environmentally compatible and have been used several times as solvent in organic synthesis.[15-18] In continuation to our work on development of green synthesis for natural products and medicinal agents[19] we wish to report here use of biomimetic catalyst cyclodextrin (CD) for C-H functionalization in water. Cyclodextrins are cyclic oligosaccharides of D(+)-glucopyranosyl units linked by α-1,4-glycosidic bonds possessing a hydrophilic outer surface and a hydrophobic central cavity which have attracted much attention as aqueous-based hosts for inclusion complex phenomena with a wide variety of guests.[20] They have substrates selective binding ability, and catalyse a wide range of chemical reactions by supramolecular catalysis, involving reversible host–guest complexes.[21-22] To the best of our knowledge, the use of β-cyclodextrin in C(sp3)-H bond functionalization of 2-alkylazaarens in aqueous medium is not reported.

Here, first time we wish to report a biomimetic, biodegradable catalyst β-cyclodextrin for C-H functionalization of 2-alkylazaarens with homo/heterocyclic diones (Scheme 1).

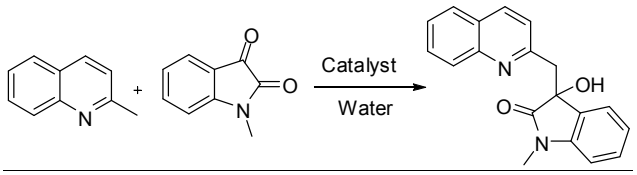
Scheme 1 Reaction of 2-Methylazaarenes with Diones



To look into the prospects of new C-C bond formation, a model reaction using easily available and reasonably priced 2-methylquinoline and 1-methylisatin was investigated in detail by varying catalysts to develop the appropriate conditions (Table 1).

The screening was initiated by using types of cyclodextrin for example α-CD, β-CD, Y-CD, β-CD-OTs and β-CD-BIMOTs to determine their catalytic efficacy. Out of all the trials, an exceedingly high product yield (91%) was obtained in the presence of β-CD (Table 1, entry 4) whereas α-CD, Y-CD, β-CD-BIMOTs gave poor yields. When the reaction was carried out without the use of catalyst, it did not provide the desired product (Table 1, entry 1). After that when the same reaction was carried

Table 1 Optimization of reaction conditions[a]



Entry	Solvent	Time(h)	Temp (°C)	Catalyst (20 mol %)	Yield (%)
1	Water	12	80	-	-
2	Water	12	100	-	-
3	Water	9	80	α-CD	22
4	Water	4	80	β-CD	91
5	Water	8	80	ϒ-CD	21
6	Water	12	80	β CD-BIMOTs	30
7	Water	14	80	β CD-Ts	17

[a]Reaction conditions: a mixture of 1a(1.0 mmol), 2a (1.2 mmol) and the catalyst (20 mol%) in the water was stirred at 80°. CD –cyclodextrin, β -CD-BIMOTs: Mono-6-deoxy-6-(3-benzylimidazolium)-β -cyclodextrin.

out without adding catalyst at higher temperature such as 100°C, no product was obtained (Table 1, entry 2) which indicate the essential role of CD in activation of C (sp3)-H bond of the 2-methylquinoline.

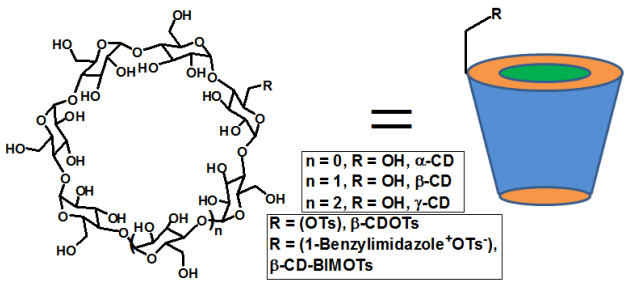


Fig. 1 Schematic representation of α -, β -, ϒ -CD and derivatives of β-CD with their equivalent truncated cone structures

Besides this we have also explored the evidence for association of 2-methylquinoline with β-CD using ^{1}H NMR spectroscopy. A comparison of ^{1}H NMR spectra (D_2O solutions) of β-CD, β-CD with 2-methylquinoline, β-CD

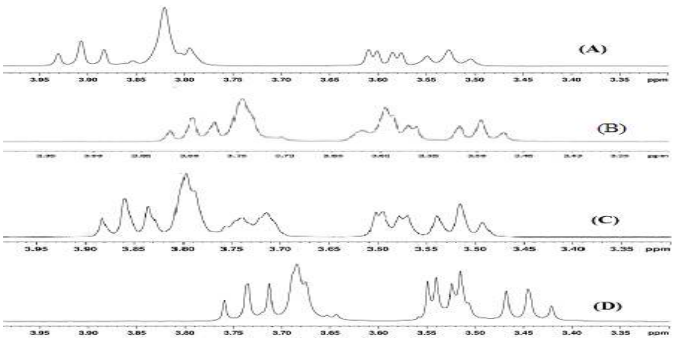
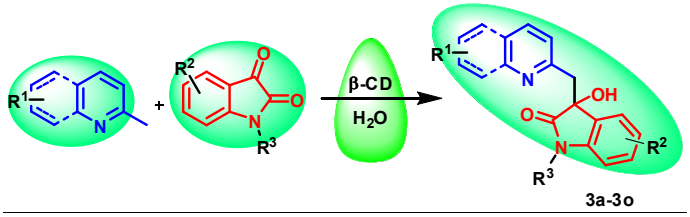


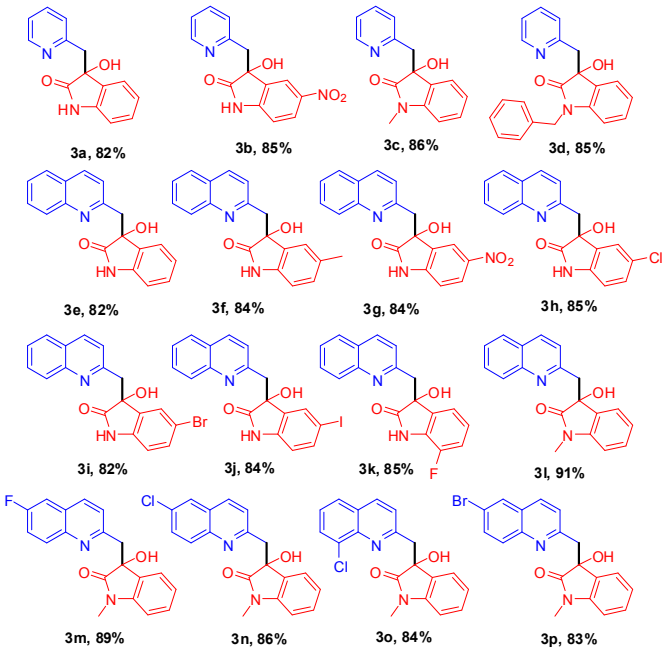
Fig. 2 ^{1}H NMR spectra of (A) β-CD (B) β-CD with 2-methylquinoline (C) β-CD with isatin (D) β-CD with isatin and 2-methylquinoline after 2 h

with isatin and β-CD with isatin and 2-methylquinoline after two hours were undertaken (Fig. 2). It is evident from Fig. 2 that there is an up field shift of protons of β-CD when complexed with 2-methylquinoline as compared to that of neat β-CD indicating the formation of an inclusion complex of 2-methylquinoline with β-CD. The up field character of protons retained in spectra of reaction mixture (after 2h) reveals the retention of complex during reaction (Fig. 2).

Intrigued by these observations and with the stipulated reaction conditions in hand, the scope and versatility of present method was extended to the reaction of 2-methylpyridine as well as 2- methylquinolines with isatins to afford a diverse range of 3-substituted-3-hydroxy-oxindoles (Scheme 2). Isatins and 2-methylquinoline with different substitution patterns participated well in the reaction to deliver the corresponding products. An increase in the yield was noticed for *N*-substituted isatins in comparison to unsubstituted one.

Scheme 2 Synthesis of azaarene-substituted 3-hydroxy-2-oxindoles



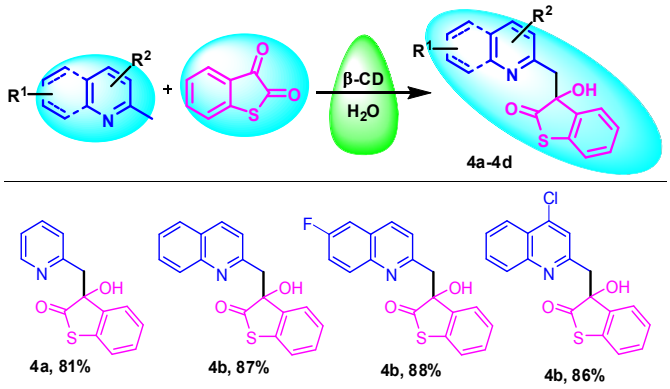


Reaction conditions: Reactions were performed with 2-methylazaarene (1.2 mmol), isatin (1.0 mmol), and β-cyclodextrin (20 mol %) in aqueous medium at 80°C.

To examine the efficacy of present greener protocol, next, it was imperative to explore the benzo [*b*] thiophene- 2, 3-

dione with 2-methylazarenes like 2-methylpyridine and 2-methylquinolines. To our delight, expected products (**4a-4d**) were obtained in good yields and the outcomes are given in Scheme 3.

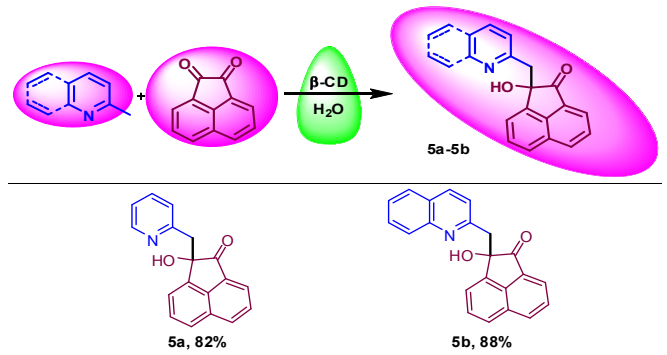
Scheme 3 Synthesis of azaarene-substituted 3-hydroxy-benzo[*b*]thiophen-2(*3H*)-ones



Reaction conditions: Reactions were performed with 2-methylazaarene (1.2 mmol), benzo[*b*]thiophene-2, 3-dione (1.0 mmol), and β-cyclodextrin (20 mol %) in aqueous medium at 80°C.

As the heterocyclic diones gave the expected results with established conditions, various homocyclic diones were subjected to the reaction with 2-methyazaarens to assess the scope and versatility of the methodology.

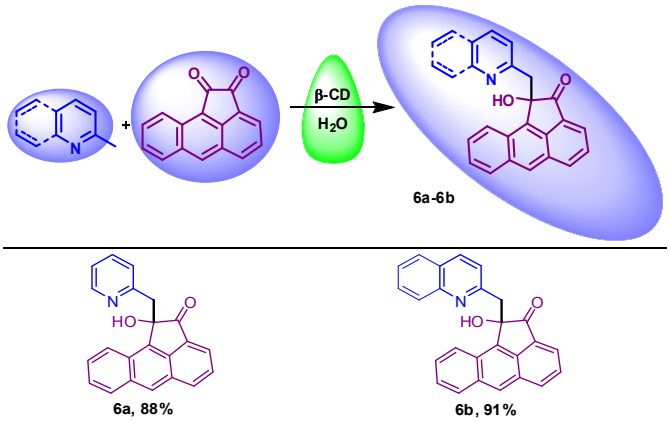
Scheme 4 Synthesis of azaarene-substituted 2-hydroxy-acenaphthylen-1(*2H*)-ones



Reaction conditions: Reactions were performed with 2-methylazaarene (1.2 mmol), acenaphthylene-1, 2-dione (1.0 mmol), and β-cyclodextrin (20 mol %) in aqueous medium at 80°C.

In this context, first we explored bicyclic. Acenaphthylene-1, 2-dione with 2-methylpyridine as well as 2-methylquinoline and desired products (**5a, 5b**) were obtained (Scheme 4). Then after, we tried the same protocol on polycyclic aceanthrylene-1, 2-dione with 2-methylpyridine as well as 2-methylquinoline and results are mentioned in Scheme 5.

Scheme 5 Synthesis of azaarene-substituted-2-hydroxyaceanthrylen-1(*2H*)-ones



Reaction conditions: Reactions were performed with 2-methylazaarene (1.2 mmol), aceanthrylene-1, 2-dione (1.0 mmol), and β-cyclodextrin (20 mol %) in aqueous medium at 80°C.

The catalyst reusability was studied five times including fresh catalyst for the synthesis of compounds **3c**, **3m**, **4b**, and **5b** and inevitable losses of catalytic activities were observed during reusability experiment (Fig. 3).

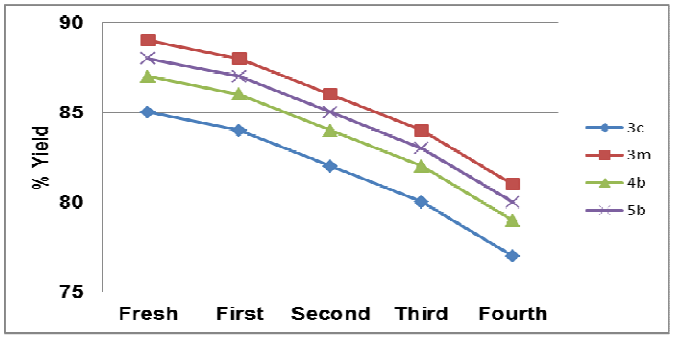


Fig. 3 Reusability data for β -cyclodextrin

A cross catalytic reusability has been studied for compounds 3c and 3m and no appreciable loss is observed. The fresh catalyst used for the synthesis of 3c is recovered and than used for synthesis of 3m for first batch synthesis and vice-versa (Fig. 4).

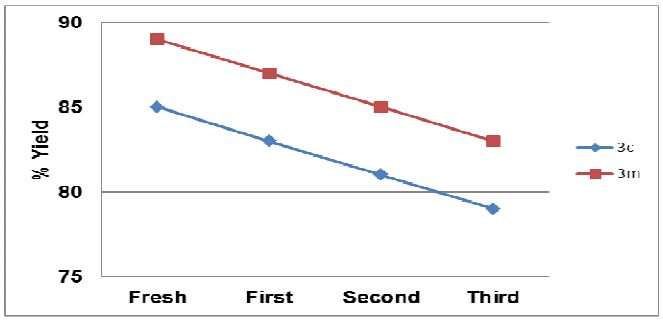


Fig. 4 Cross reusability data for β -cyclodextrin

In conclusion, we report first example of β-cyclodextrin catalysed C-H Bond functionalization of 2-methylazaarenes with various diones in water to afford 2-methylazaarene-substituted-heterocycles.This quest confers a greener route toward establishing a new horizon for C-H functionalized reactions. Furthermore, we are trying our best to exploit β-cyclodextrin in other C-H functionalized reactions in an environmental way, and the related work is underway in our laboratory.

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Notes and references

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Graphical abstract

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A β-cyclodextrin catalysed C(sp3)-H functionalization of 2-alkyl-azaarenes with homocyclic as well as heterocyclic diones in water has been developed. This bio-mimetic catalyst oriented methodology provides a sustainable protocol for C-H functionalization, the area mainly dominated by transition metals.