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# "On-water" synthesis of 3-substituted indoles via Knoevenagel/Michael addition sequence catalyzed by Cu doped ZnS NPs

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ABSTRACT

Cu doped ZnS NPs represent a green catalyst for an 'on-water' one-pot rapid synthesis of 3-substituted indole derivatives via Knoevenagel/Michael addition reaction of indane-1,3-dione, aromatic aldehydes, and indole. The catalytic activity of Cu doped ZnS NPs was about sevenfold higher as compared to the ZnS NPs. The Cu doped ZnS NPs catalyst could be recovered and reused for five reaction cycles, giving a total TOF = 201 $h^{-1}$.



A diverse array of substituted indoles beholds an arena in the field of bioactive molecules.[1] In this regard, the 3-substituted indoles and their derivatives have attracted particular attention as they are found to be the constituent of privileged motifs prevalent in various pharmaceutical and agrochemical compounds.[2] They possess a wide range of biological activity covering anticoagulant, bactericidal, neurotropic, antiphlogistic, radioprotective effects, zoocide, insecticide, and fungicide. 3-Alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives (Fig. 1).[3,4] The indane-1,3-dione moiety also represents an important bio-active motif and attracts a progressive interest of many researchers due to their widely observed biological and pharmacological properties (Fig. 1).[5]

Michael addition of heteroaromatics with electron deficient unsaturated carbonyl compounds constitutes one of the powerful methods for direct C–C bond formation.[6] They are also found to be atom efficient and thus are inherently green transformations.[7] In the past decades, the reaction has been traditionally performed with various basic catalysts or reagents, such as NaOH,[8] $Ba(OH)_2$,[9] and Mg-Al-O-*t*-Bu hydrotalcite.[10] Under the strong basic conditions side reactions, such as aldol or self-aldol addition, polymerizations, retrogressions, and rearrangements, are frequently encountered.[11] During past few years, various Lewis and Bronsted acid catalysts such as $CuBr_2$,[12] $InBr_3$,[13] $[Al(DS)_3]\cdot 3H_2O$,[14] Au(III),[15] $CeCl_3\cdot 7H_2O$–NaI,[16] $SmI_3$[17,18] and K10–FeO,[19] and metal salts have been used to catalyze Michael reaction,[20] but many of the reported procedures with homogeneous catalysts involve drawbacks such as strong acidic conditions, expensive reagents, lower yield of products, and longer reaction time. Therefore, the development of an efficient, cost-effective, and environmentally benign catalyst for Michael addition is desirable for this process.

Water is recognized as an effective reaction medium and in particular for 'on-water' reactions.[21] The unique structure and physicochemical properties of water lead to particular interactions like polarity, hydrogen bonding, hydrophobic effect, and trans-phase interactions that might greatly influence the reaction course. On one hand the hydrophobic effect has encouraging effect on the rate of reaction while hydrogen bonding has influence on reactants and transition states, which may show additive outcomes. Trans-phase interactions of water with transition states and reactants are very effectual in case of highly insoluble reactants. The water-insolubility of products further facilitates the isolation of products (or phase separation in the case of liquids). Last but not the least, due to its high heat capacity and unique redox stability, water is by far one of the most safest mediums to carry out organic reactions particularly the exothermic ones.[22] As a result, tremendous efforts have been implemented in the development of catalytic processes by employing water as a medium to accomplish greener syntheses.[23]

The fusion of a benign water medium and nano-catalyst seems to be an attractive way to develop the next generation of green and sustainable protocols.[24] Because of its high surface area and high density of active sites, nanosized metal particles exhibit superior catalytic activities compared with the corresponding bulk materials. In this context, searching for a method to incorporate the

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indole and 1,3-indanedione moieties to synthesize a hybrid framework by nanocatalytic one pot reaction in aqueous medium should be valuable and strongly desired.

Recently, we have used ZnS NPs as a heterogeneous catalyst in the synthesis of spirooxindole derivatives in water under ultrasonic irradiation.[25] In continuation of this work, we were interested in enhancing the catalytic activity of ZnS NPs. In this regard there have been few studies concerning the addition of low levels of promoters to catalysts.[26,27] Cu has been extensively investigated as a promoter element to develop new or improved catalytic system in the past.[28] Doping with copper affected measurable changes in the surface and catalytic properties of a ZnS

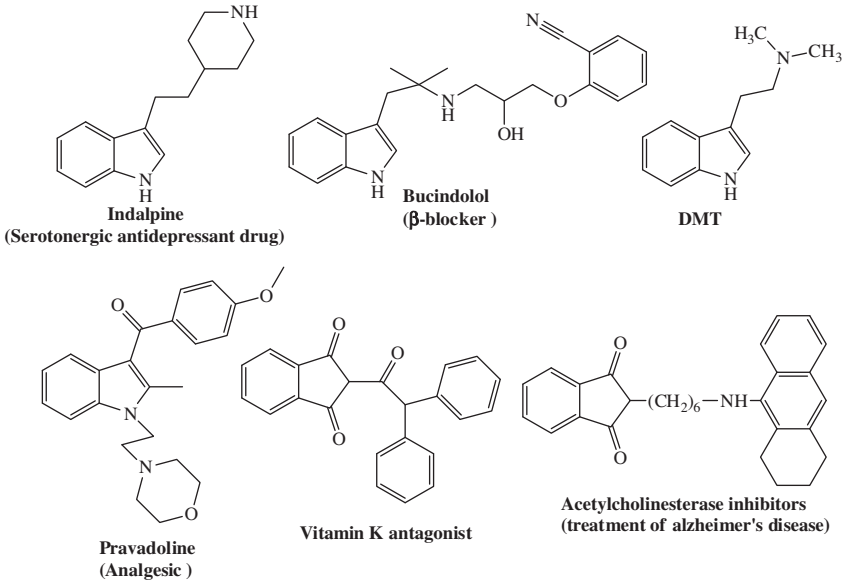
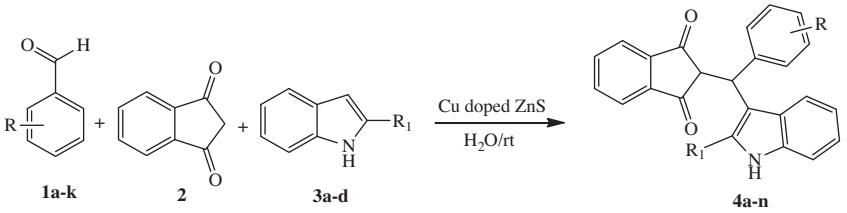
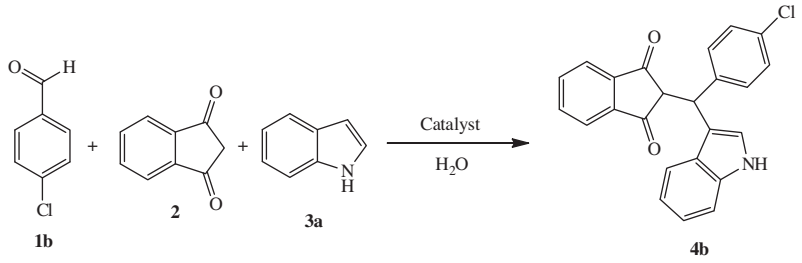



**Figure 1.** Biologically active indoles and indane-1,3-dione.




**Scheme 1.** Synthesis of novel 3-substituted indoles.

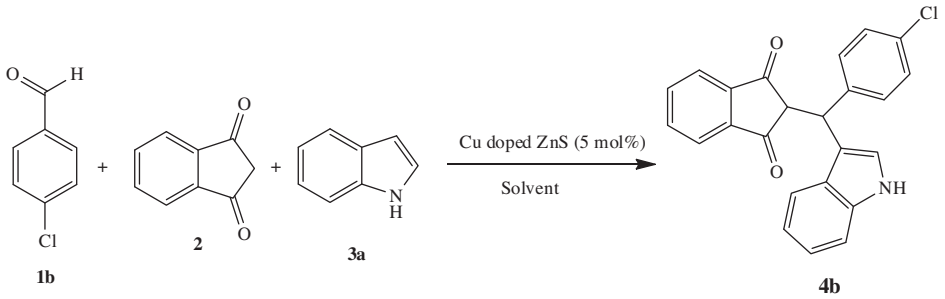
**Table 1**
Comparison of catalytic activity of catalyst for the synthesis of 2-[(4-chlorophenyl)(1*H*-indol-3-yl)methyl]-1*H*-indene-1,3(2*H*)-dione (**4b**)[a]




| Entry | Catalyst | Time (h) | Yield[b] (%) | TOF ($h^{-1}$) |
|---|---|---|---|---|
| 1 | – | 10 | NR | – |
| 2 | $ZnSO_4$ (10 mol %) | 6 | 39 | 10 |
| 3 | $ZnCl_2$ (10 mol %) | 5.5 | 43 | 12 |
| 4 | Zn dust (10 mol %) | 4.5 | 54 | 18 |
| 5 | Powder ZnS (10 mol %) | 4 | 63 | 24 |
| 6 | ZnS NPs (10 mol %) | 3.5 | 74 | 32 |
| 7 | Cu doped ZnS NPs (10 mol %) | 1.5 | 95 | 95 |
| 8 | Cu doped ZnS NPs (5 mol %) | 1.5 | 95 | 201 |

NR-no reaction.
[a] Reactions were performed on a 2 mmol scale of the reactants.
[b] Isolated yield.

**Table 2**
Effect of solvent on the synthesis of 2-[(4-chlorophenyl)(1*H*-indol-3-yl)methyl]-1*H*-indene-1,3(2*H*)-dione (**4b**)[a]



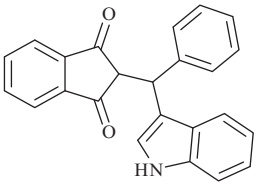
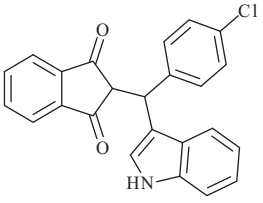
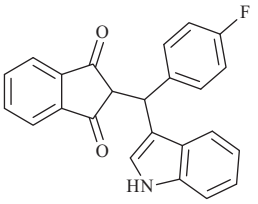
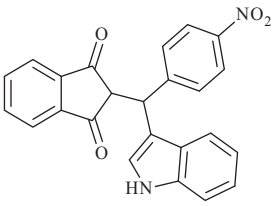

| Entry | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|
| 1 | Ethanol | 5 | 85 |
| 2 | Methanol | 6 | 81 |
| 3 | Acetonitrile | 4 | 73 |
| 4 | Toluene | 7 | 55 |
| 5 | THF | 6 | 59 |
| 6 | $CH_2Cl_2$ | 5.5 | 67 |
| 7 | Water | 1.5 | 95 |

[a] Reactions were performed on a 2 mmol scale of the reactants and 5 mol % of Cu doped ZnS at room temperature stirring.
[b] Isolated yield.

nanoparticles. A simple aqueous chemical method[25,29] has been used to prepare these nanomaterials. As a part of our continuing activities to explore novel protocols[30] for the synthesis of heterocyclic frameworks and nanomaterials, we describe herein the synthesis and characterization of Cu doped ZnS NPs, which is subsequently used for the one pot 'on water' reaction of indane-1,3-dione, aromatic aldehydes, and indole via Knoevenagel/Michael addition sequence (Scheme 1). To the best of our knowledge, this is the first Letter for the synthesis of novel 3-substituted indole scaffolds using Cu doped ZnS NPs as a reusable catalyst.

The nanostructure of the nanoparticles has been characterized by XRD, TEM, EDAX, ICP-AES, and UV–vis (Supplementary data). 2θ values of about 28.5, 47.53, and 56.34 correspond to (002), (110), and (200) planes of hexagonal phase of ZnS and the addi-

**Table 3**
Synthesis of 2-[(1*H*-indol-3-yl)(phenyl)methyl]-1*H*-indene-1,3(2*H*)-dione derivatives **4a–n**

| S. No. | R | $R_1$ | Time (h) | Product | Yield[a] (%) | MP (°C) |
|---|---|---|---|---|---|---|
| 4a | 4-H | H | 2 |  | 90 | 160–162 |
| 4b | 4-Cl | H | 1.5 |  | 95 | 242–244 |
| 4c | 4-F | H | 2 |  | 89 | 216–218 |
| 4d | 4-$NO_2$ | H | 1.5 |  | 94 | 202–204 |

(*continued on next page*)

**Table 3** (*continued*)

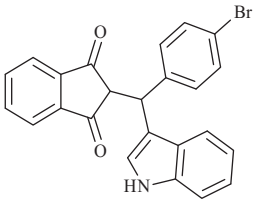
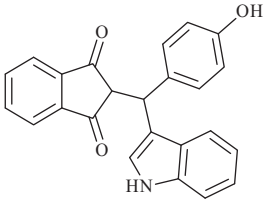
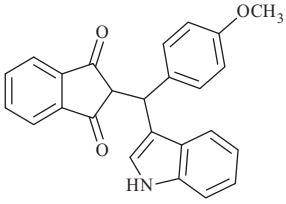
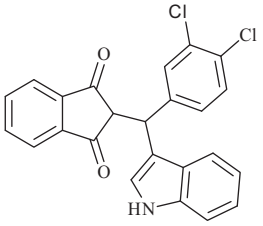
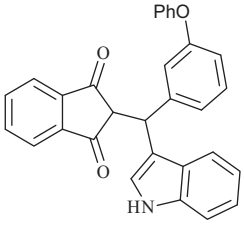
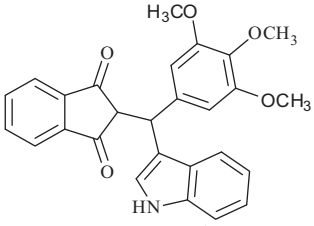
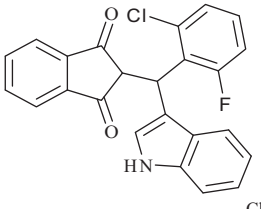
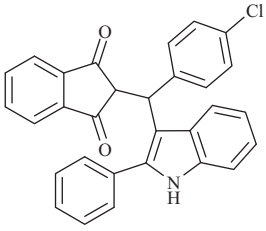
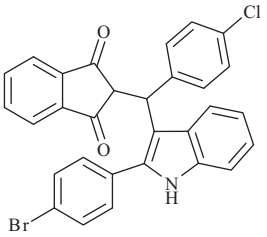
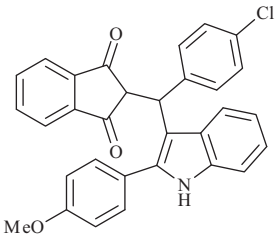
| S. No. | R | $R_1$ | Time (h) | Product | Yield[a] (%) | MP (°C) |
|---|---|---|---|---|---|---|
| 4e | 4-Br | H | 1.5 |  | 90 | 198–200 |
| 4f | 4-OH | H | 2 |  | 90 | 240–242 |
| 4g | 4-$OCH_3$ | H | 2.5 |  | 92 | 120–122 |
| 4h | 3,4-Cl | H | 1.5 |  | 91 | 238–240 |
| 4i | 3-OPh | H | 2.5 |  | 84 | 170–172 |
| 4j | 3,4,5-$(OCH_3)_3$ | H | 2.5 |  | 92 | 196–198 |
| 4k | 2-Cl-6-F | H | 1.5 |  | 91 | 186–188 |
| 4l | 4-Cl | $C_6H_5$ | 2.5 |  | 91 | 142–144 |

**Table 3** (*continued*)

| S. No. | R | $R_1$ | Time (h) | Product | Yield[a] (%) | MP (°C) |
|---|---|---|---|---|---|---|
| 4m | 4-Cl | 4-$BrC_6H_4$ | 3 |  | 88 | 148–150 |
| 4n | 4-Cl | 4-$OMeC_6H_4$ | 2 |  | 93 | 154–156 |

[a] Isolated yield.

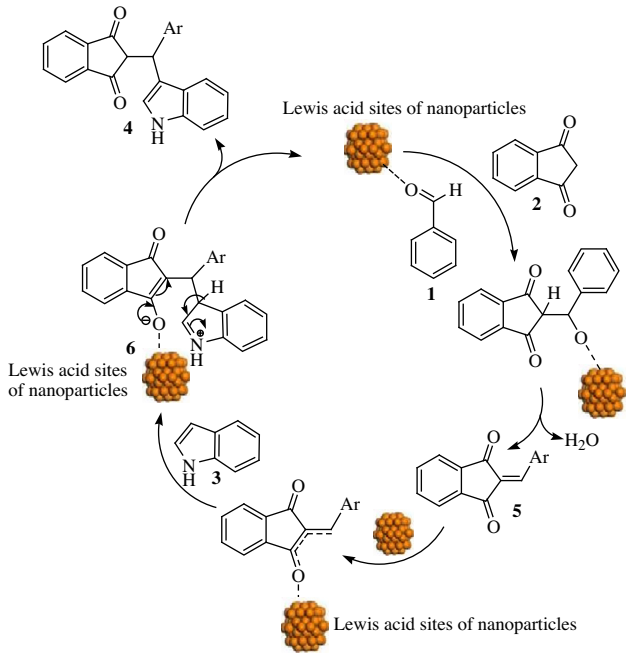
tion of Cu to ZnS nanoparticles does not create any change in the ZnS matrix (Supplementary data). The TEM images clearly indicate that the pure and Cu doped samples are nanostructured and the size of the particles is found to be in the range of 4–5 nm (Supplementary data). The size distribution of the nanoparticles has also been represented through histogram, from which it can predicted that in pure ZnS nanoparticle sample, 5 nm is a dominating size while 4.7 nm is a dominating size for Cu doped ZnS nanoparticle sample (Supplementary data).

EDAX has been employed to confirm the Cu doping in the so prepared samples of nanoparticles (Supplementary data). In UV a slight blue shift is observed with doping of Cu (Supplementary data). This shift is the outcome of the quantum confinement effect produced due to the increased nucleation rate with an increase in doping concentration.[31] The surface Lewis acidity of this material was confirmed through the adsorption of pyridine vapour[30e] on the surface of the NPs. FT-IR spectra of pyridine adsorbed on the catalysts surface are shown in Supplementary data.

In order to evaluate the catalyst efficiency of synthesized nanoparticles [32], 4-chlorobenzaldehyde **1b**, indane-1,3-dione **2,** and indole **3a** were chosen as model substrates for the reactions in water (Table 1). There is no reaction in the absence of catalyst. The reaction occurred smoothly in the presence of 10 mol % of ZnS NPs affording product in 74% yield. Further the study of catalytic ability of Cu doped ZnS nanoparticles showed that doping increases the product yield up to 95% and reduces the reaction time (1.5 h) with the decreased catalyst loading (5 mol %).[33] ZnS NPs were active in reaction with a turn-over frequency (TOF) of 32 $h^{-1}$observed. When the Cu doped ZnS NPs were used, the catalytic activity increases up to sevenfold (TOF 201 $h^{-1}$). This result is in agreement with working hypothesis that a higher concentration of acidic sites gives more products in the reaction. Therefore, the lower catalyst loading is required for this transformation as compared to many other catalytic systems. These results showed that this method is superior to the other methods in terms of yield and reaction time.

Further the analysis of the final product by ICP-AES showed that there was no nanocatalyst present in the final product. With the initial results in hand, a series of experiments were performed using various solvents, to achieve optimal reaction conditions. The superiority of water as solvent as compared to commonly employed organic solvents is quite clearly evident from the results summarized in Table 2.

Next, we examined the generality of this protocol for the synthesis of 2-[(1*H*-indol-3-yl)(phenyl)methyl]-1*H*-indene-1,3(2*H*)-dione derivatives (Table 3). After the optimal reaction conditions were established, namely, 5 mol % catalyst loading, room temperature, and use of water as solvent, the substrate generality was probed using a range of benzaldehydes. As illustrated in Table 3, various aromatic aldehydes with both electron-donating and electron-withdrawing substituents were successfully employed to prepare the corresponding product in excellent yields, the electronic factor of aromatic ring showed almost no effect on the yields. It is observed that the substitution on the 2nd position of indole nucleus gives the slightly lower yield of the final product (Table 3, en-




**Scheme 2.** Plausible mechanistic pathway.

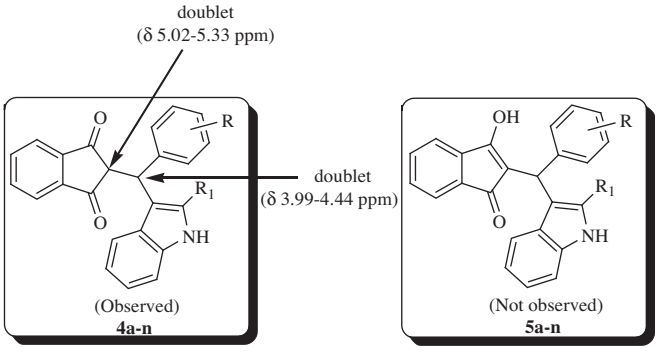



**Figure 2.** $^1$H NMR chemical shift of keto form.

tries 4l–n). Furthermore, to take advantage of the highly efficient green protocol, the reaction was scaled up to 10 mmol.

A mechanistic rationale exhibiting the probable sequence of events is given in Scheme 2. At first, NPs facilitate the Knoevenagel type coupling through Lewis acid sites coordinated to the oxygen of carbonyl groups to form α,β unsaturated ketone **5**. Activation of the α,β unsaturated ketone by Lewis acid sites of NPs facilitates nucleophilic attack of indole through its 3rd position to form an intermediate **6**, which upon subsequent electron reorganization followed by H-transfer yielded **4**, releasing the catalyst for the next cycle.

$^1$H NMR spectra of the compounds **4a–n** showed a characteristic two doublets at $\delta$ 5.07–5.33 and 4.16–4.44 ppm indicating that the products exist exclusively in their keto form,[34] which is not the case with enol form as there must be a singlet in place of two doublets (Fig. 2).

The catalyst could be recycled by simple solvent extraction of the product from the reaction mixture. For this, ethyl acetate was used, the aqueous layer containing the nanoparticles could be reused for the next cycle. The catalyst retained optimum activity till five cycles after which a drop in yield was observed. This drop might be attributed to the coagulation of nano particles which decreases the effective surface area of the catalyst (Supplementary data).

In conclusion, we have developed an 'on water' one-pot, highly efficient protocol for the synthesis of 3-substituted indoles in the presence of Cu doped ZnS NPs. The enhanced catalytic activity of ZnS NPs by Cu doping could be attributed to the increase of surface acidity. This nanocatalytic one pot reaction proceeded through Knoevenagel/Michael addition sequence. Further, the nanocatalysts were reused five times without significant loss of their catalytic activity in the same medium. The operational simplicity of this method and the purity of the recovered products make it attractive not only for the large scale synthesis of this class of biologically active molecules, but also for the synthesis of screening libraries for drug discovery as well.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.013.

## References and notes

1. (a) Jiang, B.; Yang, C.-G.; Wang, J. *J. Org. Chem.* **2001**, *66*, 4865; (b) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083.
2. (a) Zhan, Z. P.; Yang, R. F.; Lang, K. *Tetrahedron Lett.* **2005**, *46*, 3859; (c) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903; (d) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.
3. (a) Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115; (b) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635.
4. Li, J. T.; Lin, Z. P. *Ultrason. Sonochem.* **2008**, *15*, 265.
5. (a) Jubie, S.; Meena, S.; Ramaseshu, K. V.; Jawahar, N.; Vijaykumar, S. *Indian J. Chem.* **2010**, *49 B*, 1261; (b) Meena, S.; Shankar, D.; Ramseshu, K. V.; Giles, D. *Indian J. Chem.* **2006**, *45 B*, 1572.
6. (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701; (b) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218; (c) Liu, P.-M.; Chang, C.; Reddy, R. J.; Ting, Y.-F.; Kuan, H.-H.; Chen, K. *Eur. J. Org. Chem.* **2010**, 42.
7. Trost, B. M. *Science* **1991**, *254*, 1471.
8. Rehberg, R.; Kröhnke, F. *Liebigs Ann. Chem.* **1968**, *717*, 91.
9. García-Raso, A.; García-Raso, J.; Campaner, B.; Mestres, R.; Sinisterra, J. V. *Synthesis* **1982**, 1037.
10. Choudary, B. M.; Kantam, M. L.; Kavita, B.; Reddy, Ch. V.; Figueras, F. *Tetrahedron* **2000**, *56*, 9357.
11. (a) Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. *J. Mol. Catal. A: Chem.* **2008**, *292*, 44; (b) Reddy, C.; Reddy, V.; Verkade, J. G. *J. Org. Chem.* **2007**, *72*, 3093; (c) Veldurthy, B.; Clacens, J. M.; Figueras, F. *Adv. Synth. Catal.* **2005**, *347*, 767.
12. Nayak, S. K. *Synth. Commun.* **2006**, *36*, 1307.
13. Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700.
14. Firouzabadi, H.; Iranpoor, N.; Nowrouzi, F. *Chem. Commun.* **2005**, 789.
15. Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944.
16. Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594.
17. Zhan, Z.-P.; Lang, K. *Synlett* **2005**, *10*, 1551.
18. Zhan, Z.-P.; Yang, R.-F.; Lang, K. *Tetrahedron Lett.* **2005**, *46*, 3859.
19. Singh, D. U.; Singh, P. R.; Samant, S. D. *Synth. Commun.* **2006**, *36*, 1265.
20. (a) Maiti, G.; Kundu, P. *Synth. Commun.* **2007**, *37*, 2309; (b) Zhou, W.; Li, L.; Xu, L.-W.; Qiu, H.-Y.; Lai, G.-Q.; Xia, C.-G.; Castanet, A.-S. *Synth. Commun.* **2008**, *38*, 1638.
21. (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (b) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68; (c) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302; (d) Minakata, S.; Komatsu, M. *Chem. Rev.* **2009**, *109*, 711; (e) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.
22. (a) Pirrung, M. C. *Chem. Eur. J.* **2006**, *12*, 1312; (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023; (c) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809; (d) Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585; (e) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881; (f) Kommi, D. N.; Kumar, D.; Seth, K.; Chakraborti, A. K. *Org. Lett.* **2013**, *15*, 1158; (g) Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259; (h) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 2433; (i) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189; (j) Parikh, N.; Kumar, D.; Roy, S. R.; Chakraborti, A. K. *Chem. Commun.* **2011**, 1797.
23. (a) Kommi, D. N.; Kumar, D.; Chakraborti, A. K. *Green Chem.* **2013**, *15*, 756; (b) Kommi, D. N.; Jadhavar, P. S.; Kumar, D.; Chakraborti, A. K. *Green Chem.* **2013**, *15*, 798; (c) Kommi, D. N.; Kumar, D.; Bansal, R.; Chebolu, R.; Chakraborti, A. K. *Green Chem.* **2012**, *14*, 3329; (d) Chakraborti, A. K.; Rudrawar, S.; Jadhav, K. B.; Kaur, G.; Chankeshwara, S. V. *Green Chem.* **2007**, *9*, 1335; (e) Sharma, G.; Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2008**, *49*, 4269; (f) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.
24. (a) Polshettiwar, V.; Varma, R. S. *Green Chem.* **2010**, *12*, 743; (b) Seth, K.; Roy, S. R.; Pipaliya, B. V.; Chakraborti, A. K. *J. Chem. Soc., Chem. Commun.* **2013**, *49*, 5886.
25. Dandia, A.; Parewa, V.; Jain, A. K.; Rathore, K. *Green Chem.* **2011**, *13*, 2135.
26. Wang, D. S.; Li, Y. D. *Adv. Mater.* **2011**, *23*, 1044.
27. *Catalysis from A to Z, A Concise Encyclopedia*; Cornils, B., Herrmann, W. A., Schlogl, R., Wong, C. H., Eds.; Wiley-VCH: Weinheim, 2000.
28. Habimana, F.; Li, X.; Ji, S.; Lang, B.; Sun, D.; Li, C. *J. Nat. Gas Chem.* **2009**, *18*, 392.
29. John, R.; Florence, S. S. *Chalcogenide Lett.* **2010**, *7*, 269.
30. (a) Dandia, A.; Jain, A. K.; Bhati, D. S.; Laxkar, A. K. *Tetrahedron* **2013**, *69*, 2062; (b) Dandia, A.; Jain, A. K.; Sharma, S. *Tetrahedron Lett.* **2012**, *53*, 5859; (c) Dandia, A.; Jain, A. K.; Sharma, S. *Tetrahedron Lett.* **2012**, *53*, 5270; (d) Dandia, A.; Laxkar, A. K.; Singh, R. *Tetrahedron Lett.* **2012**, *53*, 3012; (e) Dandia, A.; Parewa, V.; Rathore, K. *Catal. Commun.* **2012**, *28*, 90; (f) Dandia, A.; Jain, A. K.; Bhati, D. S. *Tetrahedron Lett.* **2011**, *52*, 5333.
31. (a) Sang, W.; Quian, Y.; Min, J.; Li, D.; Wang, L.; Yinfeng, L. *Solid State Commun.* **2002**, *121*, 475; (b) Rathore, K. S.; Patidar, D. D.; Saxena, N. S.; Sharma, K. B. *J. Ovonic Res.* **2009**, *5*, 175.
32. *Cu doped ZnS NPs:* ZnS Nanoparticles were prepared at room temperature by dropping $ZnSO_4$ (50 ml, 1 M) and $Na_2S$ (50 ml, 1 M) solutions simultaneously into 200 ml of distilled water containing 50 ml of 0.1 M solution of EDTA. This was vigorously stirred using a magnetic stirrer under argon (Ar) atmosphere. The high insolubility of ZnS formed in the chemical reaction caused the formation of a number of new nuclei which prevents

the growth of already existing ones, thus limiting the particle size. The role of EDTA was to stabilize the particles against aggregation which may lead to an increase in the particle size. The doping of copper has been done by adding 3 wt% of metal sulfate ($CuSO_4{\cdot}5H_2O$) to $ZnSO_4$ (at the starting of the reaction) for the formation of ZnS:Cu NPs. The precipitate was separated from the reaction mixture and was dried at room temperature. After sufficient drying, the precipitate was crushed to fine powder with the help of mortar and pestle.

33. *General procedure for the synthesis of compounds (**4b**):* In a 50 ml round bottom flask, 4-chlorobenzaldehyde **1b** (2 mmol), indane-1,3-dione **2** (2 mmol), indole **3a** (2 mmol), and catalyst (5 mol %) were added and stirred in water (15 ml) at room temperature. The progress of the reaction was checked on TLC. After completion, the reaction mixture was extracted with ethyl acetate; the organic layer was removed under reduced pressure to afford the crude products. The pure products were obtained by recrystallization from ethanol. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, $^1$H NMR, $^{13}$C NMR, and mass spectral data).

34. *Compound **4b**:* Mp 242–244 °C; IR (KBr): $\nu_{max}$ 3376, 1715, 1740, 1454 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.98 (s, 1H, NH), 7.94 (s, 1H, CH), 7.93–6.83 (m, 12H, Ar-H), 5.16 (d, $J$ = 3.0 Hz, 1H), 4.31 (d, $J$ = 3.0 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 200.3, 199.7, 142.6, 142.4, 140.8, 137.5, 136.4, 135.4, 131.8, 129.7, 127.2, 126.7, 125.9, 124.3, 123.5, 122.6, 120.5, 119.9, 117.9, 114.4, 112.9, 112.5, 110.8, 57.7, 41.0. MS (EI, $m/z$): 386 [M+H]$^+$. *Compound **4c***: Mp 216–218 °C; IR (KBr): $\nu_{max}$ 3374, 1718, 1736, 1452 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.96 (s, 1H, NH), 7.92 (s, 1H, CH), 7.91–6.83 (m, 12H, Ar-H), 5.17 (d, $J$ = 2.4 Hz, 1H), 4.29 (d, $J$ = 2.7 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 199.9, 199.4, 162.3, 159.1, 142.2, 142.0, 137.4, 136.0, 130.4, 130.3, 126.7, 126.3, 124.2, 123.9, 122.7, 121.1, 120.8, 118.5, 118.3, 115.4, 114.7, 114.5, 114.3, 112.4, 111.4, 58.2, 34.6; MS (EI, $m/z$): 370 [M+H]$^+$. *Compound **4d***: Mp 202–204 C; IR (KBr): $\nu_{max}$ 3372, 1720, 1742, 1450 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 10.95 (s, 1H, NH), 8.33(s, 1H, CH), 8.13–6.41 (m, 12H, Ar-H), 5.31 (d, $J$ = 2.7 Hz, 1H), 4.44 (d, $J$ = 2.7 Hz, 1H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): $\delta$ 199.9, 199.3, 150.2, 146.5, 146.1, 142.4, 142.0, 136.6, 136.3, 134.6, 130.2, 129.9, 126.6, 124.8, 123.8, 123.5, 123.3, 121.7, 121.3, 119.1, 118.8, 113.4, 111.9, 111,8, 58.2, 36.2. (EI, $m/z$): 397 [M+H]$^+$.