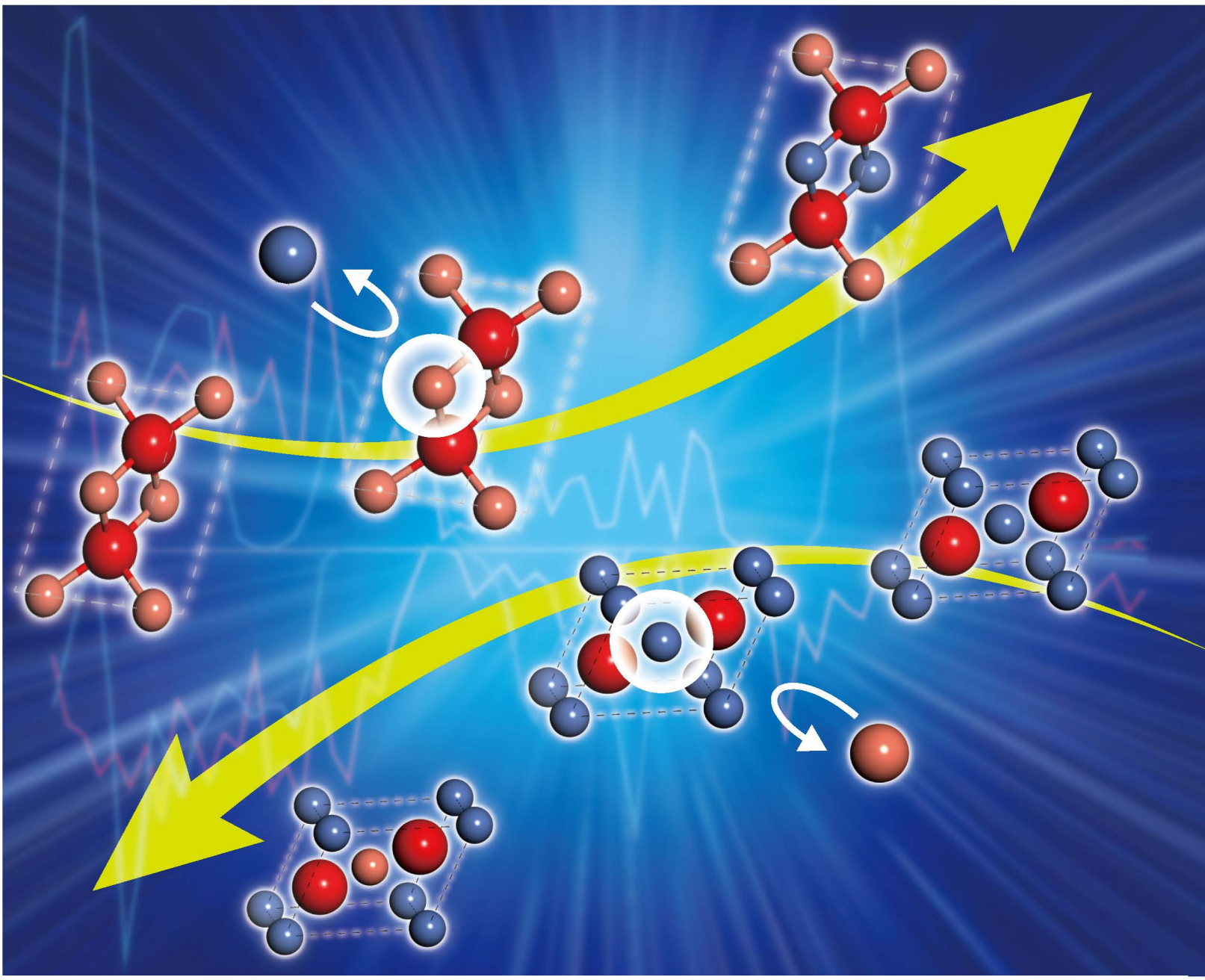
ISSN 0253-9837
CN 21-1601/O6

催化学报 Chinese Journal of Catalysis

www.cjcatal.org

Volume 38 | Number 5 | May 2017



Science Press

Editors-in-Chief Can Li (李灿) Tao Zhang (张涛)
Transaction of The Catalysis Society of China

催化学报 CHINESE JOURNAL OF CATALYSIS May 2017 Vol. 38 No. 5 pages 767–947

科学出版社

PIIJ Project for Enhancing International Impact of China STM Journals

催化学报 Chinese Journal of Catalysis

2017
Vol. 38 No. 5

Publication Monthly (12 issues)
Started in March 1980
Transaction of The Catalysis Society of China
Superintended by
Chinese Academy of Sciences
Sponsored by
Chinese Chemical Society and Dalian Institute of Chemical Physics of CAS
Editors-in-Chief Can Li, Tao Zhang
Edited by Editorial Board of
Chinese Journal of Catalysis
Published by Science Press

Distributed by Science Press
16 Donghuangchenggen North Street, Beijing 100717, China
Tel: +86-10-64017032
E-mail: sales_journal@mail.sciencep.com
Subscription Agents
Domestic All Local Post Offices in China
Foreign China International Book Trading Corporation, P.O.Box 399, Beijing 100044, China
Printed by
Dalian Haida Printing Company, Limited
Price $50

月刊 SCI收录 1980年3月创刊
中国化学会催化学会会刊

主管 中国科学院
主办 中国化学会
中国科学院大连化学物理研究所
主编 李 灿 张 涛
编辑 《催化学报》编辑委员会
出版 科 学 出 版 社

国内统一连续出版物号 CN 21-1601/O6
国际标准连续出版物号 ISSN 0253-9837
CODEN THHPD3
广告经营许可证号 2013003

总发行 科 学 出 版 社
北京东黄城根北街16号
邮编: 100717
电话: (010) 64017032
E-mail: sales_journal@mail.sciencep.com
国内订购 全国各地邮政局
邮发代号 8-93
国外订购 中国国际图书贸易总公司
北京399信箱 邮编 100044
国外发行代号 M417
印刷 大连海大印刷有限公司
定价 50元

公 开 发 行

The Fifth Editorial Board of *Chinese Journal of Catalysis*
《催化学报》第五届编辑委员会

Editorial Office Address (编辑部联系方式)

Add.: Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, Liaoning, China
Tel.: +86-411-84379240
Fax: +86-411-84379543
E-mail: cjcatal@dicp.ac.cn

地址: 大连市沙河口区中山路457号
中国科学院大连化学物理研究所
邮编: 116023
电话: (0411)84379240
传真: (0411)84379543
电子信箱: cjcatal@dicp.ac.cn

Online Submission http://www.elsevier.com/locate/chnjc
Homepage http://www.cjcatal.org

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Chinese Journal of Catalysis

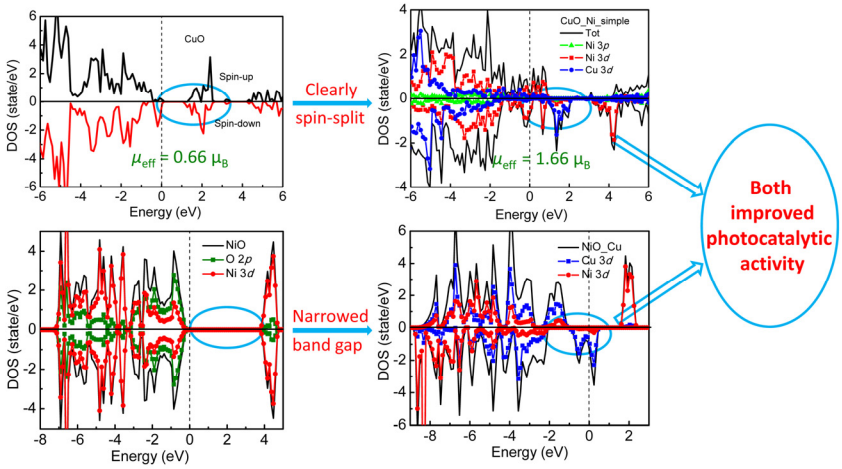
Graphical Contents

Highlights

Chin. J. Catal., 2017, 38: 767–774 doi: 10.1016/S1872-2067(17)62796-7

LSDA+*U* study on the electronic and anti-ferromagnetic properties of Ni-doped CuO and Cu-doped NiO

Yujie Li, Fan Yang *, Ying Yu *
Central China Normal University; Wuhan Textile University

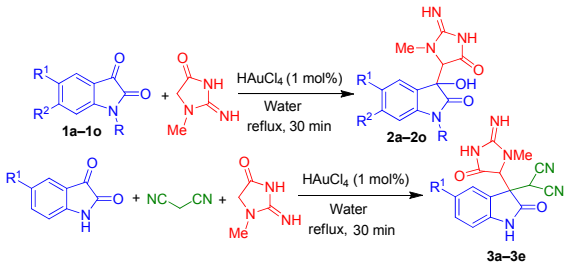


The clearly spin-split and observably narrowed band gap for the two doped semiconductor photocatalysts may benefit for the improvement of photocatalytic activity and simultaneously have a net magnetic moment for easy recycle and reuse.

Chin. J. Catal., 2017, 38: 775–783 doi: 10.1016/S1872-2067(17)62812-2

Gold-catalyzed addition reaction between creatinine and isatin: A sustainable and green chemistry approach for the diastereoselective synthesis of 3-substituted-3-hydroxyisatins

K. Parthasarathy, T. Ponpandian, C. Praveen *
Siddha Central Research Institute, Central Council for Research in Siddha (CCRS), India; Inogent Laboratories Private Limited, India; CSIR-Central Electrochemical Research Institute (CSIR-CECRI), India

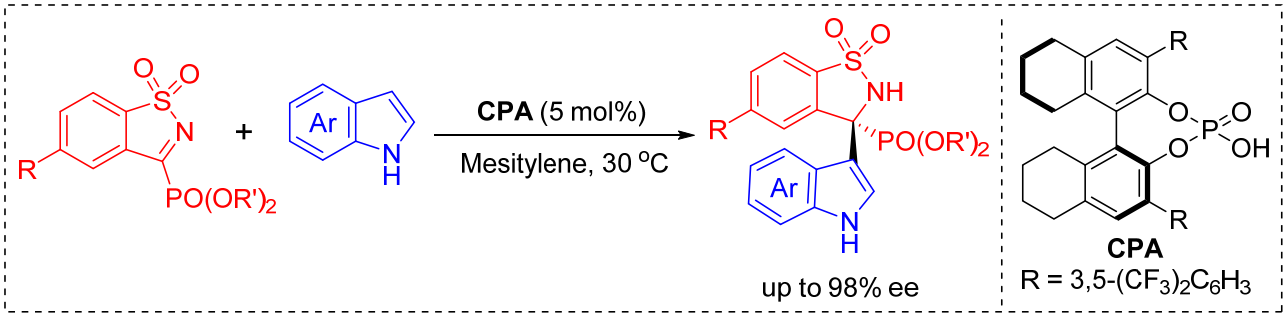


Aldolization and three component condensation of isatin derivatives with creatinine under the catalysis of auric acid in water has been developed. The synthesized compounds exhibited moderate radical scavenging activity.

Chin. J. Catal., 2017, 38: 784–792 doi: 10.1016/S1872-2067(17)62804-3

Enantioselective synthesis of quaternary α-aminophosphonates by organocatalytic Friedel–Crafts reactions of indoles with cyclic α-ketiminophosphonates

Zhong Yan, Xiang Gao, Yong-Gui Zhou *
Dalian Institute of Chemical Physics, Chinese Academy of Sciences

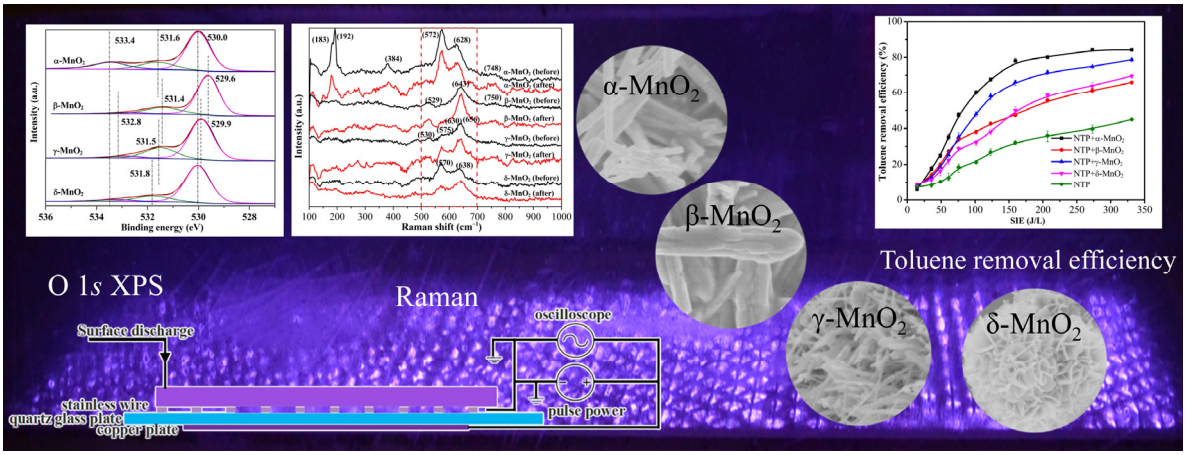


An efficient enantioselective Friedel–Crafts reaction of indoles and cyclic α-ketiminophosphonates was developed using a chiral phosphoric acid (CPA) catalyst. This reaction provides facile access to optically active quaternary α-aminophosphonates in high yields and up to 98% enantioselectivity.

Chin. J. Catal., 2017, 38: 793–804 doi: 10.1016/S1872-2067(17)62808-0

In-plasma catalytic degradation of toluene over different MnO_2 polymorphs and study of reaction mechanism

Ting Wang, Si Chen, Haiqiang Wang *, Zhen Liu *, Zhongbiao Wu
Zhejiang University; Zhejiang Provincial Engineering Research Center of Industrial Boiler & Furnace Flue Gas Pollution Control



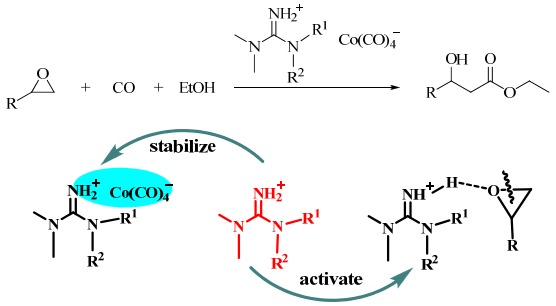
In a combined plasma-catalytic process for toluene degradation, α-MnO_2 presented the wonderful catalytic performance because of the double tunneled structure, the best stability of crystal in plasma, the Mn–O bond intension and the surface adsorbed oxygen.

Chin. J. Catal., 2017, 38: 805–812 doi: 10.1016/S1872-2067(17)62824-9

Cobalt carbonyl ionic liquids based on the 1,1,3,3-tetra-alkylguanidine cation: Novel, highly efficient, and reusable catalysts for the carbonylation of epoxides

Wei Zhang, Feng Han, Jin Tong, Chungu Xia, Jianhua Liu *
Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences

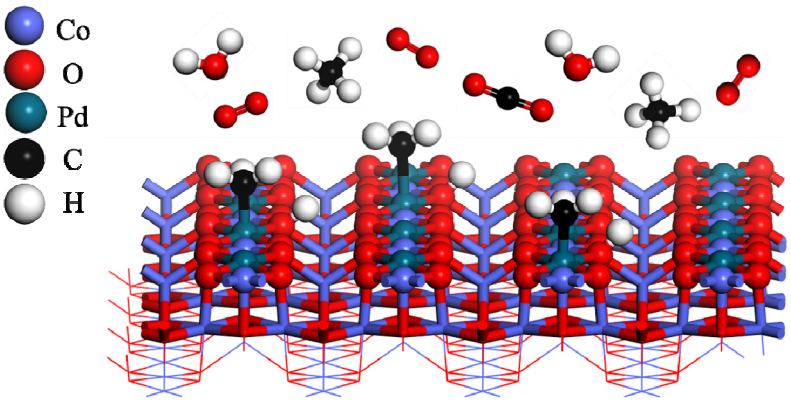
A series of novel cobalt carbonyl ionic liquids based on 1,1,3,3-tetra-alkylguanidine were synthesized. The catalytic performance of these compounds was investigated in the carbonylation of epoxides, with **3a** exhibiting the best catalytic activity and recyclability.



Chin. J. Catal., 2017, 38: 813–820 doi: 10.1016/S1872-2067(17)62817-1

Effect of Pd doping on CH_4 reactivity over Co_3O_4 catalysts from density-functional theory calculations

Chengcheng Zhao, Yonghui Zhao, Shenggang Li *, Yuhan Sun
Shanghai Advanced Research Institute, Chinese Academy of Sciences; University of Chinese Academy of Sciences; ShanghaiTech University

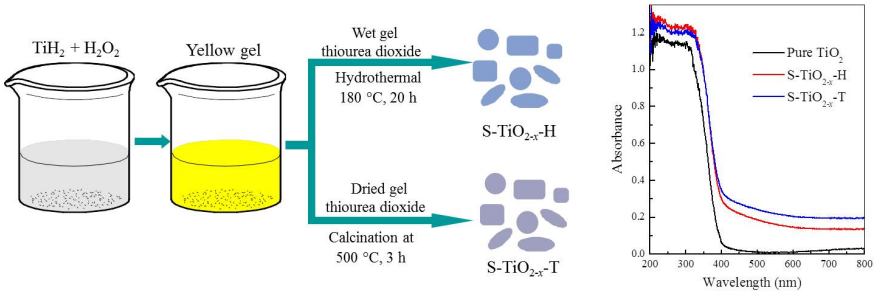


DFT calculations show that Pd-doped Co_3O_4 catalysts are more reactive for CH_4 dissociation than pure Co_3O_4 catalysts because of the much lower energy barrier and thus the higher estimated reaction rates.

Chin. J. Catal., 2017, 38: 821–830 doi: 10.1016/S1872-2067(17)62825-0

Facile synthesis of S-doped reduced TiO_{2-x} with enhanced visible-light photocatalytic performance

Zhenyu Huang, Zhenggang Gao, Shanmin Gao *, Qingyao Wang, Zeyan Wang, Baibiao Huang, Ying Dai
Ludong University; Shandong University

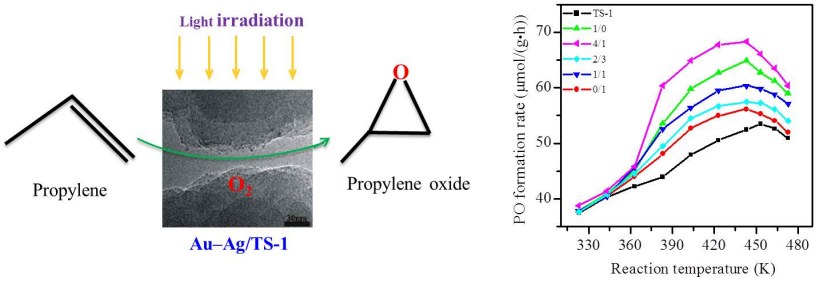


Sulfur-doped reduced titania photocatalysts were synthesized via hydrothermal treatment or calcination using thiourea dioxide as both the sulfur source and reductant. The photocatalysts absorbed visible light and displayed excellent visible-light photocatalytic performance.

Chin. J. Catal., 2017, 38: 831–844 doi: 10.1016/S1872-2067(17)62832-8

Synergetic photo-epoxidation of propylene with molecular oxygen over bimetallic Au–Ag/TS-1 photocatalysts

Naixu Li, Bin Yang, Ming Liu, Yong Chen, Jiancheng Zhou *
Southeast University; Southeast University Chengxian College

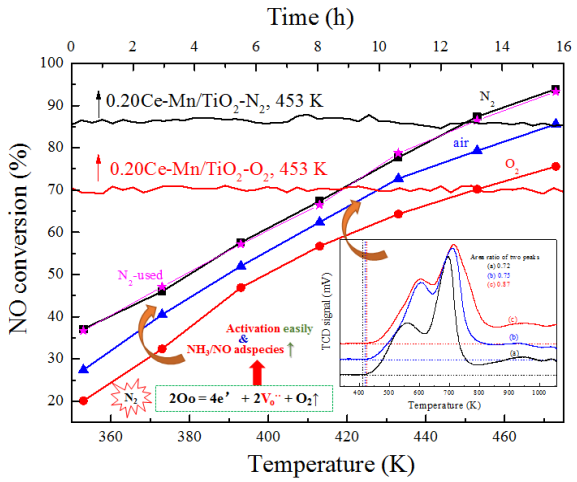


Au–Ag/TS-1 bimetallic catalysts prepared using a hydrothermal-immersion method showed a synergetic effect for photo-epoxidation of propylene using O_2 as the oxidant.

Chin. J. Catal., 2017, 38: 845–852 doi: 10.1016/S1872-2067(17)62814-6

Performance enhancement mechanism of Mn-based catalysts prepared under N_2 for NO_x removal: Evidence of the poor crystallization and oxidation of MnO_x

Kai Qi, Junlin Xie *, De Fang, Fengxiang Li, Feng He *
Wuhan University of Technology

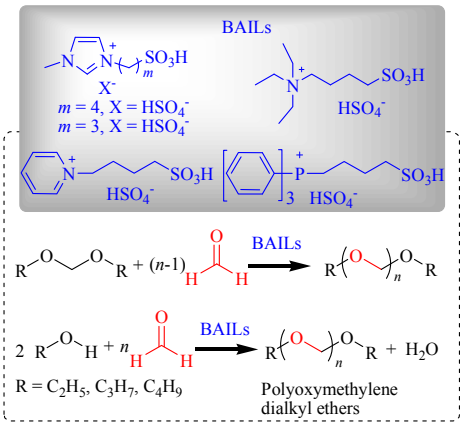


Ce-Mn/TiO_2 catalysts calcined under N_2 exhibit superior activity during NO removal, owing to a greater degree of particle dispersion, less agglomeration of particles, and a low degree of MnO_x crystallization together with low valence states, all of which favor the NH_3-SCR reactions.

Chin. J. Catal., 2017, 38: 853–861 doi: 10.1016/S1872-2067(17)62816-X

Brønsted-acidic ionic liquids as efficient catalysts for the synthesis of polyoxymethylene dialkyl ethers

Heyuan Song, Meirong Kang, Fuxiang Jin, Guoqin Wang, Zhen Li, Jing Chen *
Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences

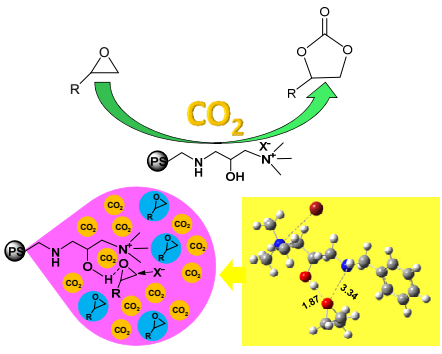


Polyoxymethylene dialkyl ethers ($RO(CH_2O)_nR$, $n \geq 1$) were synthesized by acetalation of formaldehyde with dialkyl formal or aliphatic alcohol using efficient, recyclable Brønsted-acidic ionic liquids as catalysts; excellent yields and selectivities were obtained under solvent-free conditions.

Chin. J. Catal., 2017, 38: 862–871 doi: 10.1016/S1872-2067(17)62819-5

Quaternary-ammonium-immobilized polystyrenes as efficient and reusable heterogeneous catalysts for synthesis of cyclic carbonate: Effects of linking chains and pendent hydroxyl group

Xiaoming Yan, Xuan Ding, Yu Pan, Xiaowei Xu, Ce Hao, Wenji Zheng, Gaohong He *
Dalian University of Technology

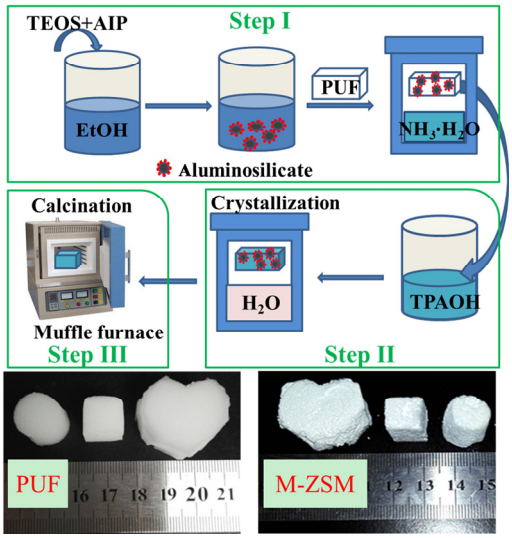


A polystyrene-supported ammonium catalyst provides larger contact area of catalysts with reactants, which enhances the reaction kinetics. A hydroxyl group on the linking chain stretches the C–O bonds of epoxides, improving the reaction thermodynamics.

Chin. J. Catal., 2017, 38: 872–878 doi: 10.1016/S1872-2067(17)62828-6

Synthesis of ZSM-5 monoliths with hierarchical porosity through a steam-assisted crystallization method using sponges as scaffolds

Tiejing Hu, Jian Liu, Changyan Cao *, Weiguo Song *
Institue of Chemistry, Chinese Academy of Sciences; University of Chinese Academy of Sciences

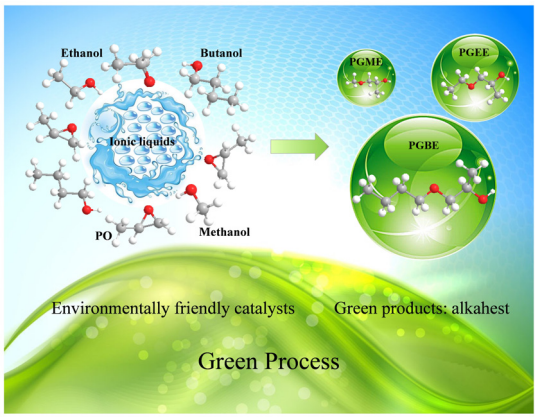


Self-supporting ZSM-5 crystals with hierarchical porosity were prepared through a steam-assisted crystallization method using sponges as rigid scaffolds. The synthesized ZSM-5 monoliths exhibited high crystallinity, hierarchical porous structures and strong acidities.

Chin. J. Catal., 2017, 38: 879–889 doi: 10.1016/S1872-2067(17)62831-6

Synthesis of propylene glycol ethers from propylene oxide catalyzed by environmentally friendly ionic liquids

Cong Zhao, Shengxin Chen, Ruirui Zhang, Zihang Li, Ruixia Liu *, Baozeng Ren, Suojing Zhang *
Zhengzhou University;
Institute of Process Engineering, Chinese Academy of Sciences;
Henan University

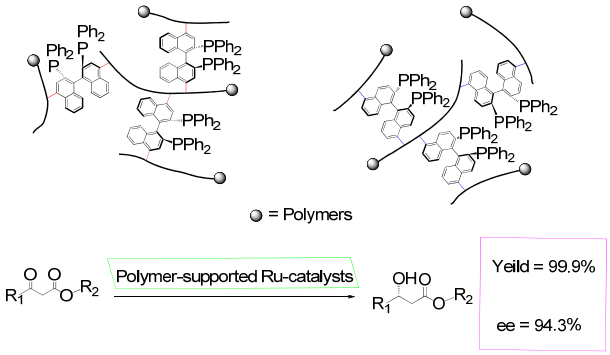


Propylene glycol ethers, namely propylene glycol methyl ether, propylene glycol ethyl ether, and propylene glycol butyl ether, were synthesized from propylene oxide and alcohols using a green process catalyzed by environmentally benign ionic liquids.

Chin. J. Catal., 2017, 38: 890–898 doi: 10.1016/S1872-2067(17)62826-2

Chiral BINAP-based hierarchical porous polymers as platforms for efficient heterogeneous asymmetric catalysis

Tao Wang, Yuan Lyu *, Kai Xiong, Wenlong Wang, Hao Zhang, Zhuangping Zhan, Zheng Jiang, Yunjie Ding *
Dalian Institute of Chemical Physics, Chinese Academy of Sciences;
University of Chinese Academy of Sciences;
Xiamen University;
Shanghai Institute of Applied Physics, Chinese Academy of Sciences

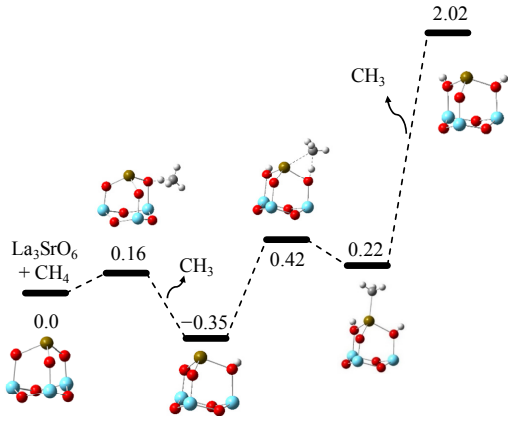


Chiral porous organic polymers were obtained *via* the copolymerization of divinyl-BINAP and divinyl benzene. The heterogeneous catalyst Ru/5-BINAP@POPs-1 exhibited good activity (yield >99%, ee = 95%) and could be reused for 6 runs in the asymmetric hydrogenation of β-keto esters.

Chin. J. Catal., 2017, 38: 899–907 doi: 10.1016/S1872-2067(17)62823-7

Sr-doping effects on La_2O_3 catalyst for oxidative coupling of methane

Linna Cong, Yonghui Zhao, Shenggang Li *, Yuhan Sun
Shanghai Advanced Research Institute, Chinese Academy of Sciences;University of Chinese Academy of Sciences; ShanghaiTech University

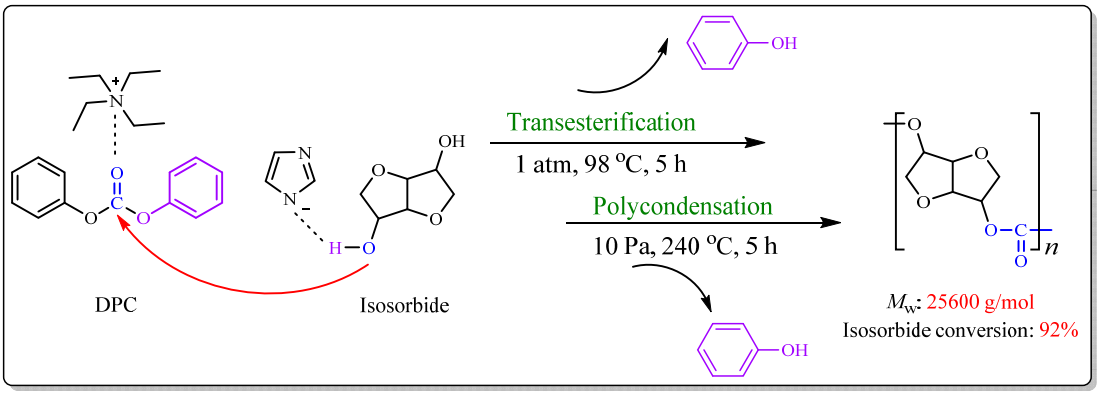


Sr dopant in a La_2O_3 catalyst can enhance its reactivity with CH_4 significantly by providing a highly reactive oxygen radical site, in addition to increasing the basicity and thus the reactivity of the non-radical metal–oxygen acid–base pair site.

Chin. J. Catal., 2017, 38: 908–917 doi: 10.1016/S1872-2067(17)62822-5

Synthesis of isosorbide-based polycarbonates via melt polycondensation catalyzed by quaternary ammonium ionic liquids

Wei Sun, Fei Xu, Weiguo Cheng, Jian Sun, Guoqing Ning *, Suojiang Zhang *
China University of Petroleum-Beijing; Institute of Process Engineering, Chinese Academy of Sciences

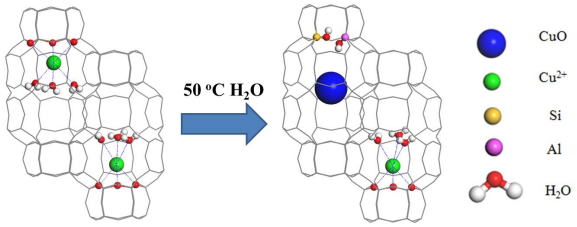


A series of quaternary ammonium ionic liquids were prepared and exhibited high catalytic activity for the synthesis of isosorbide-based polycarbonates via the melt polycondensation of diphenyl carbonate with isosorbide.

Chin. J. Catal., 2017, 38: 918–927 doi: 10.1016/S1872-2067(17)62836-5

Investigation of low-temperature hydrothermal stability of Cu-SAPO-34 for selective catalytic reduction of NO_x with NH_3

Xiao Xiang, Pengfei Wu, Yi Cao, Lei Cao, Quanyi Wang, Shutao Xu, Peng Tian *, Zhongmin Liu *
Dalian Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences

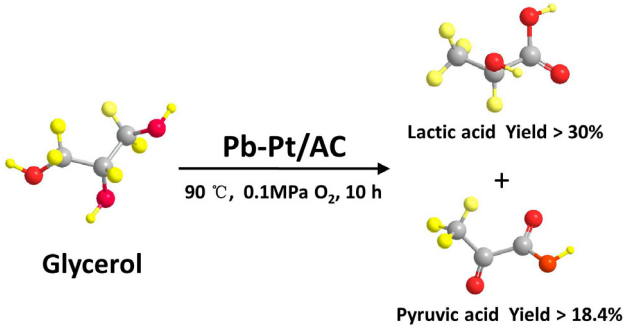


The factors that affect the low-temperature hydrothermal stability and NH_3-selective catalytic reduction performances of Cu-SPAO-34 were investigated. An understanding of these factors is important in practical applications.

Chin. J. Catal., 2017, 38: 928–938 doi: 10.1016/S1872-2067(17)62835-3

One-step synthesis of pyruvic acid from glycerol oxidation over Pb promoted Pt/activated carbon catalysts

Chen Zhang, Tao Wang *, Yunjie Ding *
Dalian Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences

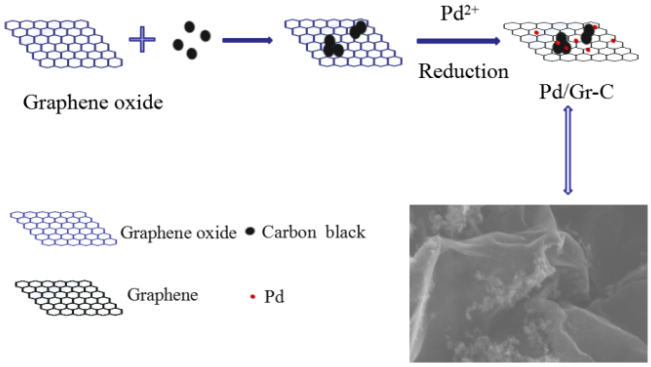


Highly dispersed Pd@Pt nanoparticles are successfully prepared via a facile and clean method at room temperature without the assistance of high-boiling point surfactant or solvent in one pot. The Pd@Pt displays remarkable ORR performance and stability.

Chin. J. Catal., 2017, 38: 939–947 doi: 10.1016/S1872-2067(17)62834-1

Enhancement of the formic acid electrooxidation activity of palladium using graphene/carbon black binary carbon supports

Meiying Lv, Wenpeng Li *, Huiling Liu, Wenjuan Wen, Guang Dong, Jinghua Liu, Kaichen Peng
Qilu University of Technology



Composite catalysts consisting of Pd loaded on binary graphene/carbon black supports were synthesized by a reduction method. These materials exhibit better electrocatalytic performance than either Pd/carbon black or Pd/graphene catalysts, suggesting a new approach to binary carbon supports for noble metal-based catalysts with fuel cell applications.

中国科学院科学出版基金资助出版

催化学报 Chinese Journal of Catalysis

月刊SCI收录2017 年 5 月第 38 卷 第 5 期

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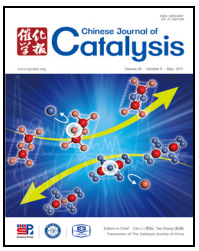


Article

Gold-catalyzed addition reaction between creatinine and isatin: A sustainable and green chemistry approach for the diastereoselective synthesis of 3-substituted-3-hydroxyisatins

K. Parthasarathy [a], T. Ponpandian [b], C. Praveen [c,*]

[a] *Department of Chemistry, Siddha Central Research Institute, Central Council for Research in Siddha (CCRS), Arumbakkam, Chennai-600106, Tamil Nadu, India*

[b] *Inogent Laboratories Private Limited, Industrial Development Area Nacharam, Hyderabad-500076, Telangana, India*

[c] *Functional Materials Division, Council of Scientific and Industrial Research-Central Electrochemical Research Institute (CSIR-CECRI), Karaikudi-600006, Tamil Nadu, India*

ARTICLE INFO

Article history:
Received 5 January 2017
Accepted 28 February 2017
Published 5 May 2017

Keywords:
Creatinine
Gold catalysis
Green chemistry
Diastereoselectivity
Antioxidant

ABSTRACT

The aldolization of various isatins with creatinine under gold catalysis in water has been developed. The reaction is operationally simple as the products can be isolated by simple filtration without requiring tedious solvent extraction and column chromatographic techniques. The generality of this methodology is showcased through the reactions of a wide range of isatin derivatives with creatinine to afford the respective aldol products in excellent yields with complete *syn*-selectivity. The scope of this chemistry is further extended to a tandem reaction involving isatins, creatinine and malononitrile to afford multicomponent products in excellent yields with complete *anti*-selectivity. The antioxidant potency of the synthesized compound was assessed by a spectrophotometric method, which revealed that three compounds containing halogen atoms (**2c**, **2d** and **2e**) were the most active compared with the standard.

1. Introduction

The structural motif of 3-substituted-3-hydroxyisatin is present in several bioactive natural products as well as clinical drugs such as paratunamide A, CPC-1 and sporidesmin (Fig. 1) [1–3]. The medicinal properties of these compounds are derived from the C3 substituent and the absolute configuration of the chiral center [4]. The development of efficient and practical methods to prepare such compounds is of paramount importance and it is an active area of research in asymmetric catalysis [5–7]. One of the simplest preparative procedures for 3-substituted-3-hydroxyisatins is the catalytic addition of nucleophiles to readily available isatins, which grants access to appealing molecular scaffolds possessing quaternary carbon centers [8,9]. Furthermore, organic reactions employing water as a medium hold great promise from a green chemistry perspective [10]. For example, Dash *et al.* [11,12] have previously reported the water-catalyzed diastereoselective aldol reaction of thiazolidinediones with isatin and other aldehydes. As part of our ongoing interest in developing new methodologies for the synthesis of heterocycles [13–24], coupled with the reality that creatinine is present in numerous natural products [25], we envisaged the replacement of thiazolidinediones with structurally relevant creatinine in the aldolization of isatins. In 2010, Crooks *et al.* [26–29] reported the diastereoselective aldol addition of isatins with creatinine. However, this methodology

* Corresponding author. Tel: +91-9677733808; E-mail: chandrasekar.praveen@gmail.com
DOI: 10.1016/S1872-2067(17)62812-2| http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 38, No. 5, May 2017

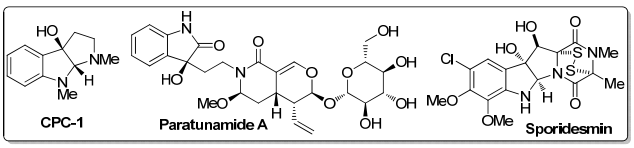


Fig. 1. Natural products containing a 3-hydroxyisatin scaffold.

suffers from the need to use $NaOOCH_3$ (NaOAc) and CH_3COOH (AcOH) in stoichiometric quantities, which prompted us to revisit this transformation with particular emphasis on performing the reaction under gold catalysis in water without compromising the diastereoselectivity. Herein, we report our study on the gold(III)-catalyzed diastereoselective aldol addition of isatins with creatinine under aqueous condition leading to 3-hydroxyisatin derivatives. In view of the extensive biological properties of 3-hydroxyisatins, all the compounds were screened for their free radical scavenging activity. The gold-catalyzed protocol was also extended to a three-component reaction between isatins, malononitrile and creatinine through a tandem condensation / conjugate addition.

2. Experimental

2.1. Materials, methods and instruments

Solvents and reagents were purchased from SRL chemicals, India Pvt. Ltd, India and were used without further purification. Melting points (m.p.) were determined in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a Jasco FT-IR spectrophotometer as KBr pellets. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 solutions on a Bruker spectrometer at 400 and 100 MHz, respectively. The proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.00$) as internal standard and are expressed in parts per million (ppm). The spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). The coupling constants (J) are given in hertz. Mass spectra were recorded on a PE-SCIEX API 3000 mass spectrometer. Elemental analyses were recorded using a ThermoFinnigan FLASH EA 1112CHN analyzer. All compounds gave C, H and N analysis within ±0.5% of the theoretical values. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany) using analytical grade solvents and visualized with iodine spray (10% (w/w) I_2 in silica gel) or UV light (λ = 254 and 365 nm). The absorbance was measured at 517 nm using a Systronics 118 model spectrophotometer.

*2.2. General procedure for the synthesis of compounds **2a**–**2p***

Water (15 mL) was added to a mixture of 1.0 mmol of isatin derivative, 1.2 mmol of creatinine (for **2p**, 2.3 mmol of creatinine) and 1 mol% of $HAuCl_4$ and the resulting suspension was heated to reflux for 30 min. The clear reaction mixture was cooled to 15–20 °C. The precipitated aldol product was filtered and washed with copious amount of water and then with methanol and ethyl acetate (EtOAc). The obtained product was thoroughly dried under vacuum to afford the pure product **2a**–**2p**.

3-Hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2a**): Yellow solid; m.p. = 225–227 °C; IR (KBr): 3557, 3384, 3242, 2795, 1718, 1689, 1672, 1242, 755 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.14 (s, 3H, $-CH_3$), 4.04 (s, 1H, CH), 6.31 (brs, 1H, OH), 6.70–6.74 (d, J = 7.6 Hz, 1H, $-C_7H$), 6.81–6.88 (t, J = 7.6 Hz, 1H, $-C_6H$), 7.06–7.07 (d, J = 7.6 Hz, 1H, $-C_4H$), 7.17–7.20 (t, J = 7.8 Hz, 1H, $-C_5H$), 7.51 (brs, 2H, NH_2), 10.23 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.6, 69.4, 76.3, 109.5, 121.1, 123.9, 127.9, 129.3, 142.6, 171.8, 175.7, 182.3. MS (ESI): m/z = 261 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.38%; H, 4.65%; N, 21.53%. Found C, 55.55%; H, 4.61%; N, 21.45%.

5-Fluoro-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2b**): Pale yellow solid; m.p. = 250–252 °C; IR (KBr): 3358, 3174, 3047, 2697, 1731, 1701, 1645, 1435, 806 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.14 (s, 3H, CH_3), 4.07 (s, 1H, CH), 6.52 (bs, 1H, OH), 6.70–6.75 (m, 1H, $-C_7H$), 6.80–6.84 (dd, J = 8.1 Hz, J = 2.37 Hz 1H, $-C_4H$), 6.99–7.06 (m, 1H, $-C_6H$), 7.51 (brs, 2H, NH_2), 10.28 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.2, 69.8, 76.5, 111.0, 124.2, 126.0, 129.9, 130.4, 141.9, 172.7, 175.8, 182.1. MS (ESI): m/z = 279 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{11}FN_4O_3$: C, 51.80%; H, 3.98%; N, 20.14%. Found C, 52.09%; H, 3.92%; N, 20.05%.

5-Chloro-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2c**): Pale brown solid; m.p. = 267–269 °C; IR (KBr): 3384, 3177, 2782, 2672, 1731, 1707, 1618, 1586, 1083, 818 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (s, 3H, CH_3), 4.07 (s, 1H, CH), 6.52 (brs, 1H, OH), 6.74–6.77 (d, J = 8.1 Hz, 1H, $-C_7H$), 6.99–7.00 (d, J = 2.4 Hz, 1H, $-C_4H$), 7.23–7.24 (dd, J = 8.1 Hz, J = 2.1 Hz, 1H, $-C_6H$), 7.55 (brs, 2H, NH_2), 10.39 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.8, 69.6, 76.3, 110.9, 123.9, 125.0, 129.1, 129.9, 141.6, 172.0, 175.3, 182.1. MS (ESI): m/z = 295 $[M+H]^+$, 297 $[M+H]^{2+}$; Anal. Calcd. for $C_{12}H_{11}ClN_4O_3$: C, 48.91%; H, 3.76%; N, 19.01%. Found C, 49.05%; H, 3.72%; N, 18.94%.

5-Bromo-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2d**): Brown solid; m.p. = 246–248 °C; IR (KBr): 3384, 3176, 2980, 2672, 1731, 1707, 1566, 1186, 818 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.16 (s, 3H, CH_3), 4.07 (s, 1H, CH), 6.53 (brs, 1H, OH), 6.70–6.73 (d, J = 8.1 Hz, 1H, $-C_6H$), 7.11 (s, 1H, $-C_4H$), 7.36–7.38 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H, $-C_7H$), 7.76 (brs, 2H, NH_2), 10.42 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.9, 69.6, 76.4, 111.5, 112.7, 126.6, 130.4, 132.0, 142.1, 172.1, 175.2, 182.1. MS (ESI): m/z = 339 $[M+H]^+$, 241 $[M+H]^{2+}$; Anal. Calcd. for $C_{12}H_{11}Br_4O_3$: C, 42.50%; H, 3.27%; N, 16.52%. Found C, 42.35%; H, 3.33%; N, 16.60%.

5-Iodo-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2e**): Dark brown solid; m.p. = 202–204 °C; IR (KBr): 3394, 3176, 2973, 2768, 1730, 1707, 1583, 1308, 1184, 817 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.17 (s, 3H, CH_3), 4.06 (s, 1H, CH). 6.44 (brs, 1H, OH), 6.66–6.71 (d, J = 8.4 Hz, 1H, $-C_6H$), 7.09 (s, 1H, $-C_4H$), 7.37–7.40 (dd, J = 8.2 Hz; J = 1.4 Hz, 1H, $-C_7H$), 7.13 (s, 1H, $-C_4H$), 7.44–7.49 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H, $-C_7H$); ^{13}C NMR (DMSO-d_6): δ 33.0, 69.8, 76.5, 111.5, 112.8, 126.9, 130.4, 132.2, 142.3, 172.5, 175.5, 182.6. MS (ESI): m/z = 387 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{11}IN_4O_3$: C, 37.32%; H, 2.87%;

N, 14.51%. Found C, 37.51%; H, 2.81%; N, 14.44%.

5-Nitro-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2f**): Dark yellow solid; m.p. > 300 °C; IR (KBr): 3421, 3345, 3190, 2922, 1734, 1707, 1583, 1313, 1207, 846 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.23 (s, 3H, CH_3), 4.15 (s, 1H, CH), 6.74 (s, 1H, OH), 6.95–6.98 (d, J =8.7 Hz, 1H, –C_7H), 7.67 (bs, 2H, NH_2), 7.83–7.84 (d, J =2.7 Hz, 1H, –C_4H), 7.81–7.82 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H, –C_7H), 11.04 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 33.1, 69.9, 75.8, 109.8, 119.2, 126.9, 128.9, 141.5, 149.4, 172.3, 176.0, 181.9. MS (ESI): m/z = 305 $[M+H]^+$; Anal. Calcd. for $C_{12}H_{12}N_5O_5$: C, 47.22%; H, 3.63%; N, 22.94%. Found C, 46.99%; H, 3.68%; N, 23.04%.

3-Hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-1-methylindolin-2-one (**2g**): Pale yellow solid; m.p. = 230–232 °C; IR (KBr): 3603, 3384, 3174, 2884, 1722, 1711, 1648, 1102, 754 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.05 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 4.10 (s, 1H, CH), 6.45 (brs, 1H, OH), 6.91–6.97 (m, 2H, -C_5H, –C_6H), 7.07–7.09 (d, J = 7.5 Hz, 1H , C_7H), 7.25–7.31 (t, J = 8.1 Hz, 1H, –C_4H), 7.55 (brs, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 25.9, 32.6, 69.9, 76.3, 109.2, 111.2, 115.9, 129.0, 140.4, 156.4, 171.9, 174.0, 181.9. MS (ESI): m/z = 275 $[M+H]^+$; Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93%; H, 5.14%; N, 20.43%. Found C, 57.08%; H, 5.09%, N, 19.99%.

3-Hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-1-ethylindolin-2-one (**2h**): Pale yellow solid; m.p. = 196–198 °C; IR (KBr): 3603, 3381, 3176, 2985, 1726, 1710, 1698, 1338, 1102, 754 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.32 (t, J = 7.6 Hz, 3H, CH_2), 3.12 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 4.15 (s, 1H, CH), 6.52 (brs, 1H, OH), 6.88–6.94 (m, 2H, –C_5H, –C_6H), 7.07–7.09 (d, J = 7.6 Hz, 1H , C_7H), 7.27–7.33 (t, J = 8.1 Hz, 1H, –C_4H), 7.64 (brs, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 19.1, 25.9, 32.9, 70.5, 76.3, 109.7, 111.9, 115.4, 129.0, 140.8, 156.8, 172.3, 174.5, 182.5. MS (ESI): m/z = 289 $[M+H]^+$; Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32%; H, 5.59%; N, 19.43%. Found C, 57.99%; H, 5.65%; N, 19.60%.

3-Hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-1-hexylindolin-2-one (**2i**): Pale yellow solid; m.p. = 183–185 °C; IR (KBr): 3366, 3314, 3173, 3063, 2956, 1696, 1652, 1498, 763 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.87 (t, J = 7.6 Hz, 3H, –CH_3), 1.22–1.35 (m, 6H, –$(CH_2)_3$–Me), 1.40–1.44 (m, 2H, –CH_2–); 3.25 (s, 3H, NMe), 3.44 (t, J = 7.6 Hz, 2H); 4.22 (s, 1H, CH), 5.99 (brs, 1H, OH), 6.95 (d, J = 8.4 Hz, 1H, ArH); 7.19–7.24 (m, 2H, ArH), 7.36–7.41 (m, 1H, ArH) 7.77 (brs, 2H, –NH_2). ^{13}C NMR (DMSO-d_6): δ 13.9, 21.9, 26.5, 27.2, 28.1, 31.4, 44.4, 77.7, 88.4, 115.4, 125.2, 125.7, 127.7, 128.9, 144.5, 159.2, 174.1, 179.9. MS (ESI): m/z = 345 $[M+H]^+$; Anal. Calcd. for $C_{18}H_{24}N_4O_3$: C, 62.77%; H, 7.02%; N, 16.27%. Found C, 63.01%; H, 6.96%; N, 16.20%.

3-Hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-1-phenylindolin-2-one (**2j**): Pale yellow solid; m.p. = 229–231 °C; IR (KBr): 3402, 3199, 2948, 1722, 1700, 1132, 843 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.25 (s, 3H, CH_3), 4.22 (s, 1H, CH), 6.62 (brs, 1H, OH), 6.64–6.65 (d, J = 0.6 Hz, 1H, C_4H), 6.98-7.03 (t, J = 7.6 Hz, 1H, Ar–H), 7.17–7.23 (m, 2H, C_5H, C_6H), 7.44–7.60 (m, 5H, Ar-H, C_7H), 7.70 (brs, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 33.0, 70.6, 76.3, 108.9, 122.7, 124.4, 126.9, 127.1, 127.2, 128.1, 129.6, 129.7, 129.9, 134.4, 143.9, 171.9, 174.1, 182.5. MS (ESI): m/z = 337 $[M+H]^+$; Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 64.28%; H, 4.79%; N, 16.66%. Found C, 63.99%; H, 4.71%; N, 16.57%.

1-Benzyl-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2k**): Pale brown solid; m.p. = 207–209 °C; IR (KBr): 3377, 3312, 3199, 3065, 3031, 2824, 1705, 1644, 1575, 1215, 798 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.20 (s, 3H, NMe), 4.04 (s, 1H, CH), 5.22 (s, 2H, –CH_2Ph), 6.21 (brs, 1H, OH), 6.93 (d, J = 7.6 Hz, 1H, ArH), 7.19–7.27 (m, 5 H, ArH), 7.34–7.39 (m, 3H), 7.69 (brs, 2H, NH_2). ^{13}C NMR (DMSO-d_6): δ 35.1, 55.5, 83.3, 94.1, 118.1, 124.7, 126.0, 127.0, 127.9, 128.4, 128.5, 147.5, 171.2, 175.1, 180.9. MS (ESI): m/z = 351 $[M+H]^+$; Anal. Calcd. for $C_{19}H_{18}N_4O_3$: C, 65.13%; H, 5.18%; N, 15.99%. Found C. 64.95%; H, 5.25%; N, 16.11%.

1-Acetyl-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2l**): Colorless solid; m.p. = 175–177 °C; IR (KBr): 3603, 3381, 3175, 2985, 2939, 1727, 1710, 1698, 1649, 1375, 754 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.58 (s, 3H, -$COCH_3$), 3.23 (s, 3H, CH_3), 4.24 (s, 1H, CH), 6.77 (brs, 1H, OH), 7.17–7.38 (m, 3H, C_4H, C_5H, C_6H), 7.46 (brs, 1H, NH), 7.56 (brs, 1H, NH), 8.04–8.06 (d, J = 8.1 Hz, 1H, C_7H); ^{13}C NMR (DMSO-d_6): δ 26.1, 32.9, 71.0, 76.3, 117.3, 123.9, 128.7, 129.2, 129.7, 139.1, 169.9, 172.3, 175.4, 181.9. MS (ESI): m/z = 303 $[M+H]^+$; Anal. Calcd. for $C_{14}H_{14}N_4O_4$: C, 55.63%; H, 4.67%; N, 18.53%. Found C, 55.75%; H, 4.65%; N, 18.45%.

1-Benzoyl-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2m**): Colorless solid; m.p. = 224–226 °C; IR (KBr): 3600, 3380, 3166, 2989, 2925, 1730, 1709, 1700, 1645, 1379, 755 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.17 (s, 3H, CH_3), 4.21 (s, 1H, CH), 4.74–4.91 (ABq, J = 16.2 Hz), 6.57 (brs, 1H, OH), 6.64–6.67 (d, J = 8.1 HZ, 1H, -C_4H), 6.91–6.96 (t, J = 7.6 Hz, 1H, –C_5H), 7.11–7.34 (m, 5H, –C_6H, –C_7H and Ar–H), 7.45–7.47 (d, J = 7.2 Hz, 2H, Ar–H), 7.56 (brs, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 32.7, 42.9, 69.5, 76.0, 109.0, 121.9, 123.7, 127.0, 127.2, 127.3, 127.4, 128.2, 128.3, 129.4, 136.0, 143.2, 171.9, 174.4, 182.3. MS (ESI): m/z = 365 $[M+H]^+$; Anal. Calcd. for $C_{19}H_{18}N_4O_3$: C, 62.63%; H, 4.43%; N, 15.38%. Found C, 62.75%; H, 4.38%; N, 15.30%.

3-Hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-1-(phenylsulfonyl)indolin-2-one (**2n**): Colorless solid; m.p. = 230–232 °C; IR (KBr): 3444, 3389, 3267, 2968, 1768, 1725, 1701, 1682, 1544, 1108, 858 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.13 (s, 3H, CH_3), 4.17 (s, 1H, CH), 6.93 (brs, 1H, OH), 7.15–7.17 (m, 2H, C_5H, C_6H), 7.36–7.42 (m, 2H, Ar–H), 7.62–7.84 (m, 5H, Ar–H, NH_2), 8.05–8.08 (m, 2H, C_4H, C_7H); ^{13}C NMR (DMSO-d_6): δ 33.32, 70.7, 78.3, 122.4, 124.3, 124.5, 126.9, 127.0, 127.1, 128.3, 128.4, 129.5, 135.4,142.1, 171.9 (C=N), 173.9, 182.6. MS (ESI): m/z = 401 $[M+H]^+$; Anal. Calcd. for $C_{18}H_{16}N_4O_5S$: C, 53.99%; H, 4.03%; N, 13.99%; S, 8.01%. Found C, 60.11%; H, 3.99%; N, 14.07%; S 7.95%.

5,6-Dibromo-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2o**): Brown solid; m.p. = 196–198 °C; IR (KBr): 3391, 3350, 3246, 3176, 2782, 2607, 1731, 1706, 1585, 1477, 1082, 818 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.17 (s, 3H, CH_3), 4.10 (s, 1H, CH), 6.69 (brs, 1H, OH), 7.10 (s, 1H, –C_6H), 7.52 (brs, 1H, NH), 7.67 (d, 1H, J = 1.8 Hz, –C_4H), 7.85 (bs, 1H, NH), 10.80 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 32.9, 69.8, 77.0, 102.8, 113.2, 125.7, 131.6, 133.9, 141.7, 172.2, 175.1,

181.9. MS (ESI): m/z = 417 $[M+H]^+$, 419 $[M+H]^{2+}$, 421 $[M+H]^{4+}$; Anal. Calcd. for $C_{12}H_{10}Br_2N_4O_3$: C, 34.48%, H, 2.41%, N, 13.40%. Found C, 34.59%; H, 2.36%; N, 13.33%.

1,1'-(Propane-1,3-diyl)bis(3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one (**2p**): Pale brown solid; m.p. > 300 °C; IR (KBr): 3361, 3189, 1708, 1644, 1467, 1200, 755 cm^{-1}; mp 287–289 °C; ^1H NMR (DMSO-d_6): δ 1.55–1.61 (m, 2H), 3.01 (s, 3H, NMe), 4.02 (t, J = 7.6 Hz, 4H), 4.27 (s, 2H, CH), 6.05 (brs, 2H, OH), 7.00 (d, 2H, J = 8.4 Hz, Ar–H), 7.21 (d, 2H, J = 8.4 Hz, Ar–H), 7.29–7.42 (m, 4H, Ar–H), 7.83 (brs, 2H, NH), 9.89 (brs, 2H, NH). ^{13}C NMR (DMSO-d_6): δ 22.9, 35.7, 39.9, 82.1, 90.7, 115,1, 124.2, 124.8, 126.7, 127.1, 142.6, 153.8, 174.7, 179.9. MS (ESI): m/z = 561 $[M+H]^+$; Anal. Calcd. for $C_{27}H_{28}N_8O_6$: C, 57.85%; H, 5.03%; N, 19.99%. Found C, 58.04%; H, 4.99%; N, 19.82%.

*2.3. General procedure for the synthesis of compounds (**3a**–**3e**)*

A mixture of 1.0 mmol of isatin, 1.0 mmol of malononitrile and 1 mol% of chloroauric acid in 15 mL of water was stirred at room temperature for 15 min. To this mixture was added 1.2 mmol of creatinine and the resulting suspension was heated to reflux for 30 min and then cooled to room temperature. The precipitated product was filtered and washed with copious amount of water and then with methanol and ethyl acetate. The obtained product was thoroughly dried under vacuum to afford the crude product. The crude product was purified by column chromatography using hexane/EtOAc eluent system to afford the inseparable diastereoisomeric mixture of **3a**–**3e**.

2-(3-(2-Imino-3-methyl-5-oxoimidazolidin-4-yl)-2-oxoindolin-3-yl)malononitrile (**3a**): Pale yellow solid; m.p. = 201–203 °C; IR (KBr): 3324, 2912, 2255, 1725, 1702, 1305, 877 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.33 (s, 3H, NMe), 4.34 (CH–CO), 5.93 (s, 1H, $CH(CN)_2$), 6.96 (d, J = 6.0 Hz, 1H), 7.15 (s, 1H, ArH), 7.40 (s, 1H, ArH), 7.49 (s, 1H, ArH), 7.50 (brs, 1H, –NH), 8.03 (brs, 1H, –NH), 11.07 (brs, 1H, NH–CO). ^{13}C NMR (DMSO-d_6): δ 33.2, 43.9, 53.3, 66.1, 111.0, 111.6, 112.3, 123.1, 124.5, 125.0, 131.4, 142.8, 172.7, 173.4, 183.1. MS (ESI): m/z = 309 $[M+H]^+$; Anal. Calcd. for $C_{15}H_{12}N_6O_2$: C, 58.44%; H, 3.92%; N, 27.26%. Found C, 58.89%; H, 3.85%; N, 27.10%.

2-(5-Fluoro-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-2-oxoindolin-3-yl)malononitrile (**3b**): Colorless solid; m.p. = 165–167 °C; IR (KBr): 3329, 2922, 2233, 1717, 1632, 1314, 799 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.50 (s, 3H, NCH_3), 4.38 (s, 1H, CH-CO), 5.95 (s, 1H, $CH(CN)_2$), 6.96–6.99 (m, 1H, ArH), 7.25–7.32 (m, 2H, ArH), 7.59 (brs, 1H, NH), 8.07 (brs, 1H, NH), 11.11 (brs, 1H, NH–CO). ^{13}C NMR (DMSO-d_6): δ 33.3, 53.6, 66.1, 111.2, 111.8, 112.3, 112.4 ($J_{C\text{-}F}$ = 32.0 Hz), 112.6, 118.0, 118.2, 126.0, 139.1, 157.2, 159.6 ($J_{C\text{-}F}$ = 152.0 Hz), 172.6, 173.0, 182.7. MS (ESI): m/z = 327 $[M+H]^+$; Anal. Calcd. for $C_{15}H_{11}FN_6O_2$: C, 55.22%; H, 3.40%; N, 25.76%. Found C, 54.90%; H, 3.45%; N, 25.91%.

2-(5-Chloro-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-2-oxoindolin-3-yl)malononitrile (**3c**): Colorless solid; m.p. = 189–191 °C; IR (KBr): 3325, 2978, 2248, 1728, 1699, 1344, 813 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H, NCH_3), 4.39 (s, 1H, CH–CO), 5.98 (1H, s, $CH(CN)_2$), 6.98 (d, J = 6.9 Hz, 1H, ArH), 7.46 (d, J = 8.3 Hz, 2H, ArH), 7.62 (brs, 1H, NH), 8.09 (brs, 1H, NH), 11.22 (brs, 1H, NH–CO). ^{13}C NMR (DMSO-d_6): δ 27.0, 53.0, 66.0, 111.0, 111.6, 112.1, 124.3, 126.1, 126.5, 130.9, 141.5, 172.1, 173.2, 182.3. MS (ESI): m/z = 343 $[M+H]^+$, 345 $[M+H]^{2+}$; Anal. Calcd. for $C_{15}H_{11}ClN_6O_2$: C, 52.56%; H, 3.23%; N, 24.52%. Found C, 52.90%; H, 3.17%; N, 24.41%.

2-(5-Nitro-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)-2-oxoindolin-3-yl)malononitrile (**3d**): Dark yellow solid; m.p. = 297–299 °C; IR (KBr): 3308, 2951, 2251, 1701, 1689, 1378, 798 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.68 (s, 3H, $-NCH_3$), 4.48 (s, 1H, CH–CO), 6.15 (s, 1H, $CH(CN)_2$), 7.19 (d, J = 8.4 Hz, 1H, ArH), 8.16–8.55 (m, 2H, ArH), 9.31 (brs, 1H, NH), 10.17 (brs, 1H, NH), 11.87 (brs, 1H, NH–CO). ^{13}C NMR (DMSO-d_6): δ 34.0, 52.7, 66.9, 110.9, 111.5, 120.3, 124.9, 128.1, 142.4, 149.2, 173.0, 174.0, 182.1. MS (ESI): m/z = 354 $[M+H]^+$; Anal. Calcd. for $C_{15}H_{11}N_7O_4$: C, 50.99%; H, 3.14%; N, 27.75%. Found C, 51.22%; H, 3.08%; N, 27.60%.

2-(3-(2-Imino-3-methyl-5-oxoimidazolin-4-yl)-5-methyl-2-oxoindolin-3-yl)malononitrile (**3e**): Light yellow solid; m.p. = 213–215 °C; IR (KBr): 3301, 2934, 2250, 1711, 1678, 1311, 843 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, $-CH_3$), 2.39 (s, 3H, $-NCH_3$), 4.29 (s, 1H, CH–CO), 5.90 (s, 1H, $CH(CN)_2$), 6.86 (d, J = 7.1 Hz, 1H, ArH), 7.21 (d, J = 6.92 Hz, 1H, ArH), 7.33 (s, 1H, ArH), 7.49 (brs, 1H, NH), 8.00 (brs, 1H, NH), 10.95 (brs, 1H, NH–CO). ^{13}C NMR (DMSO-d_6): δ 21.1, 22.3, 44.0, 53.3, 66.0, 110.8, 111.6, 112.3, 125.0, 131.6, 132.2, 140.3, 172.6, 173.2, 183.2. MS (ESI): m/z = 323 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{14}N_6O_2$: C, 56.92%; H, 4.38%; N, 26.07%. Found C, 57.05%; H, 4.32%; N, 25.99%.

*2.4. General procedure for the determination of radical scavenging activity of 3-hydroxyisatins (**2a**–**2o**) by the DPPH method*

To a 3 mL ethanolic solution of 1,1-diphenyl-2-picryl-hydrazil (DPPH, 200 μmol/L), 0.05 mL of different concentration (50, 500, 1000 μg/mL) of test samples and 20 μg of ascorbic acid were added. The solutions were incubated at 37 °C for 30 min. The absorbance was measured at 517 nm using a Systronics 118 model spectrophotometer. The percentage inhibition of the DPPH radical was calculated by comparing the results of the test with those of the control using the formula: inhibition (%) = $(A_C - A_T)/A_C \times 100$, where A_C is the absorbance of the control sample and A_T is the absorbance of test sample.

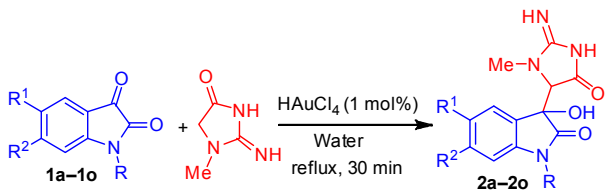
*2.5. General procedure for the hydrogen peroxide radical scavenging activity of 3-hydroxyisatins (**2a**–**2o**)*

Hydrogen peroxide radical scavenging activity was performed by dissolving 10 μg of each 3-hydroxyisatin (**2a**–**2o**) in 3.4 mL of 0.1 mol/L phosphate buffer (pH = 7.4) and mixing with 600 μL of 43 mmol/L solution of H_2O_2. butylated hydroxy toluene (BHT, 20 μg) was used as a standard and the stock solution was prepared in the same buffer. The absorbance value (230 nm) of the reaction mixture was recorded at 10 min intervals between 0 and 40 min. For each concentration, a blank sample was used for background subtraction. The percentage of inhibition was calculated by comparing the results of the test

with those of the control using the formula: inhibition (%) = (A_C – A_T)/A_C × 100, where A_C is the absorbance of the control sample and A_T is the absorbance of test sample.

3. Results and discussion

Before commencing our studies, we took into consideration that commonly used gold precatalysts are either unstable ($AuCl_3$) or sparingly soluble (AuCl and $AuBr_3$) in water. Therefore, our attention was focused on the use of chloroauric acid ($HAuCl_4$), which happens to be the precursor for most of the commercially available gold salts. A mixture of isatin **1a**, creatinine and chloroauric acid (1 mol%) in water was heated to reflux (Scheme 1). Even though, the starting materials were not completely soluble in water, the pure product **2a** was obtained after 30 min, as confirmed by NMR analysis (Table 1, entry 1). Most importantly, the product was obtained stereoselectively as a single diastereoisomer, which was in sharp agreement to Crook's protocol [26]. As chloroauric acid undergoes hydrolysis in water to form HCl and subsequently catalyze the whole process, a control experiment with substrate **1a** was performed by using a 10% HCl solution. After 30 min at reflux temperature, only 10% of the product **2a** was formed, as indicated by NMR analysis of the crude product. Screening with other potentially oxophilic catalysts such as $Zn(OTf)_2$, $Cu(OTf)_2$ and $In(OTf)_3$ under similar conditions did not lead to the formation of the product. Pleased with these initial results, we applied chloroauric acid as a catalyst for the reaction of a range of isatin derivatives. Isatin derivatives possessing substituents with a different electronic nature on the nitrogen as well as on the periphery were tolerated and gave excellent yields of the aldol product **2a**–**2o** (Table 1). All the reactions were performed in completely demineralized water (pH = 7) as slight acidity or basicity of the reaction medium could also influence the stereochemical outcome. A blank reaction without chloroauric acid did not proceed at all. One of the beneficial advantages of our protocol is that products with a bromo or an iodo substituent (**2d**, **2e** and **2o**) could also be realized. These could potentially serve as synthetic precursors for organometallic cross-coupling reactions [30]. The structural characterization of all the products was established from their spectral data (FTIR, ^{1}H NMR, ^{13}C NMR and MS) and elemental analyses. As an illustrative example, the IR spectrum of compound **3a** exhibited sharp peaks at 1718 and 1689 cm^{-1} corresponding to the carbonyl stretching of oxindole and creatinine cores, respectively. Broad stretching bands between 3384 and 3314 cm^{-1} suggested the presence of various amide functionalities. A broad parabolic peak between 3557 and 3444 cm^{-1} revealed the presence of an



Scheme 1. Au(III)-catalyzed aldolization of isatins with creatinine in water.

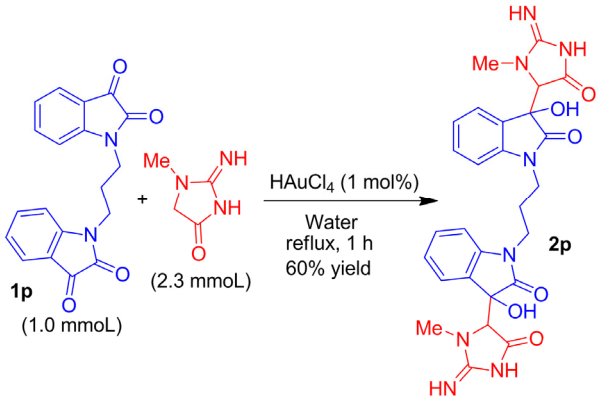
Table 1
Synthesis of 3-substituted-3-hydroxyisatins.

Entry	R	R^1	R^2	Product [a]	Yield [b] (%)
1	H	H	H	**2a**	95
2	H	F	H	**2b**	94
3	H	Cl	H	**2c**	94
4	H	Br	H	**2d**	95
5	H	I	H	**2e**	81
6	H	NO_2	H	**2f**	90
7	Me	H	H	**2g**	96
8	Et	H	H	**2h**	97
9	Hexyl	H	H	**2i**	95
10	Ph	H	H	**2j**	92
11	Bn	H	H	**2k**	98
12	Ac	H	H	**2l**	91
13	Bz	H	H	**2m**	94
14	SO_2Ph	H	H	**2n**	92
15	H	Br	Br	**2o**	91

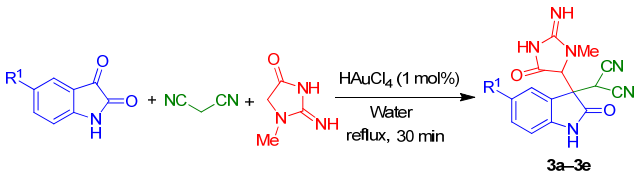
[a] All products were characterized by IR, NMR and MS.
[b] Isolated yield of products after filtration.

intermolecularly bonded hydroxyl group. The ^{1}H NMR spectrum recorded in DMSO-d_6 showed a singlet at δ = 4.04 ppm, which corresponded to the 4'-methyne hydrogen and a broad singlet at 6.31 ppm, which indicated the presence of a hydroxyl group, which was D_2O exchangeable. In the ^{13}C NMR spectrum, peaks at 175.7 and 182.3 ppm indicated the presence of the carbonyl carbons of isatin and creatinine, respectively. Additionally, the peaks at 69.4 and 76.3 ppm were assigned to the tertiary aliphatic carbon and quaternary carbon (the carbons of the bond between the isatin and creatinine moieties), respectively. Finally, the mass spectrum exhibited a molecular ion peak at m/z = 261 $[M+H]^+$, which strongly supported the formation of product **2a**. The exclusive diastereoselectivity (an equimolar mixture of *SS* and *RR* isomers) of **2a** can be explained by the Zimmerman-Traxler model, which favors *anti*-selective products over the *syn*-isomers [31].

Up to this point, we have only discussed the aldolization chemistry of monosubstituted systems. We also used our methodology for the synthesis of more complex systems. As depicted in Scheme 2, we applied our gold(III)-catalyzed procedure for the synthesis of a complex bis-isatinyl system **1p**. Thus, treatment of 1,1'-(propane-1,3-diyl)bis-isatin (1.0 mmol) with creatinine (2.3 mmol) under our optimized conditions



Scheme 2. Au(III)-catalyzed aldolization of bis-isatin **1p** with creatinine in water.



Scheme 3. Au(III)-catalyzed multi-component reaction of isatins, malononitrile and creatinine.

Table 2
Synthesis of adducts **3a–3e**.

Entry	R^1	Product [a]	Yield [b] (%)
1	H	**3a**	87
2	F	**3b**	90
3	Cl	**3c**	88
4	NO_2	**3d**	91
5	Me	**3e**	83

[a] All products were characterized by IR, NMR and MS.
[b] Isolated yield of products after filtration.

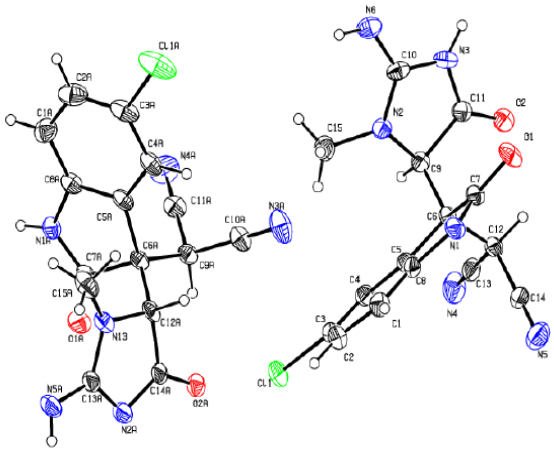


Fig. 2. ORTEP diagram of the X-ray crystal structure of compound **3c**.

produced the corresponding bis-aldol product **2** in 60% yield after reflux for 1 h.

In an attempt to display the synthetic embellishment of our chemistry, we probed the reaction of several isatins with malononitrile and creatinine to realize a sequential condensation/Michael addition (Scheme 3). The reaction resulted in the formation of multicomponent adducts **3a**–**3e** in satisfactory yields (Table 2).

All products were thoroughly characterized by performing spectroscopic analysis. For example, the ^{1}H NMR spectrum of compound **3c** exhibited singlets at δ = 5.98 and 4.39 ppm, which correspond to the CH-proton of the $CH(CN)_2$ group and creatinine moieties, respectively. In the ^{13}C NMR spectrum, the peaks at δ = 43.9 and 66.1 ppm corresponded to the carbon flanked by the geminal cyano groups and the tertiary carbon of the creatinine core, respectively. In the mass spectrum, two Cl isotope peaks at m/z = 343 $[M+H]^+$ and 345 $[M+H]^{2+}$ confirmed the formation of product **3c**. To establish the stereochemistry of the products, a single crystal of **3e** was obtained and used for X-ray diffraction. Analysis of the crystal structure revealed that compound **3e** was formed as the *anti*-isomer (*R*,*R* and *S*,*S* enantiomeric pairs) and no *syn*-stereochemistry was observed (Fig. 2). The exclusive formation of the *anti*-isomer over *syn*-isomer was in contrast to our aldolization study.

Because of our continuing interest in chemical biology [32–48] coupled with the information about radical scavenging properties of isatin derivatives [49], we investigated the antioxidant potency of the isatin derivatives **2a**–**2o** by DPPH radical scavenging and hydrogen peroxide methods. The radical scavenging activity [50] of 3-hydroxy isatins was determined spectrophotometrically [51] by using Blois's protocol [52]. All compounds were tested for their interaction with stable free radical DPPH, which specifies their radical scavenging activity. The percentage of inhibition was compared with that of standard L-ascorbic acid (Table 3). The results as a percentage (%) are expressed as the ratio of absorbance decrease at 517 nm and the absorbance of DPPH solution in the absence of compounds. A lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The capability to scavenge the DPPH radical was calculated using the equation: DPPH

Table 3
Radical scavenging activity of 3-hydroxyisatins (**2a–2o**) by the DPPH method.

No.	Sample	At 50 μg/mL		At 500 μg/mL		At 1000 μg/mL	
		Absorbance	Activity (%)	Absorbance	Activity (%)	Absorbance	Activity (%)
1	L-Ascorbic acid	0.035	96	0.026	97	0.008	99
2	**2a**	0.721	19	0.329	63	0.213	76
3	**2b**	0.704	21	0.427	52	0.276	69
4	**2c**	0.721	19	0.302	66	0.133	85
5	**2d**	0.739	17	0.463	48	0.178	80
6	**2e**	0.704	21	0.311	65	0.115	87
7	**2f**	0.668	25	0.374	58	0.213	76
8	**2g**	0.650	27	0.320	64	0.267	70
9	**2h**	0.802	10	0.686	23	0.516	42
10	**2i**	0.757	15	0.516	42	0.240	73
11	**2j**	0.695	22	0.401	55	0.222	75
12	**2k**	0.873	02	0.784	12	0.579	35
13	**2l**	0.666	26	0.375	58	0.219	75
14	**2m**	0.720	19	0.330	64	0.215	77
15	**2n**	0.649	27	0.319	64	0.269	69
16	Control			0.8913			

Table 4
Radical scavenging activity of 3-hydroxyisatins (**2a–2o**) by the H_2O_2 method.

No.	Sample	At 0 min		At 10 min		At 20 min		At 30 min		At 40 min	
		Absorbance	Activity (%)	Absorbance	Activity (%)	Absorbance	Activity (%)	Absorbance	Activity (%)	Absorbance	Activity (%)
1	BHT	0.072	92	0.126	86	0.153	83	0.162	82	0.180	80
2	**2a**	0.514	43	0.586	35	0.712	21	0.799	20	0.757	16
3	**2b**	0.126	86	0.135	85	0.234	74	0.252	72	0.279	69
4	**2c**	0.108	88	0.135	85	0.216	76	0.243	73	0.270	70
5	**2d**	0.063	93	0.144	84	0.162	82	0.207	77	0.261	71
6	**2e**	0.153	83	0.162	82	0.171	81	0.180	80	0.189	79
7	**2f**	0.144	84	0.153	83	0.180	80	0.243	73	0.288	68
8	**2g**	0.162	82	0.171	81	0.234	74	0.261	71	0.315	65
9	**2h**	0.387	57	0.514	43	0.550	39	0.631	30	0.712	21
10	**2i**	0.135	85	0.180	80	0.162	82	0.225	75	0.315	65
11	**2j**	0.117	87	0.153	83	0.225	75	0.270	70	0.369	59
12	**2k**	0.360	60	0.487	45	0.541	45	0.586	35	0.685	24
13	**2l**	0.145	84	0.150	84	0.189	81	0.245	72	0.295	67
14	**2m**	0.117	87	0.153	83	0.225	75	0.270	70	0.369	59
15	**2n**	0.145	84	0.155	83	0.181	80	0.245	74	0.281	66
16	Control					0.9022					

scavenging effect (%) = $(A_c - A_t/A_c) \times 100$, where A_c is the absorbance of the control reaction and A_t is the absorbance in the presence of samples or standards. Analysis of the screening results revealed that the radical scavenging activity of the compounds on DPPH radicals increases with respect to the concentration (Table 3). Compounds possessing 5-Cl (**2c**), 5-Br (**2d**) and 5-I (**2e**) moieties showed maximum activity at a concentration of 1000 μg/mL. This could be attributed to the better homolysis tendency of the carbon–halide bond leading to the respective free radicals. The radical scavenging activity of compounds possessing N-Et (**2h**) and N-Bn (**2k**) groups was less potent compared with the standard. Hydrogen peroxide radical scavenging activity [50] was performed using a solution of hydroxyisatins **2a**–**2o** in a mixture of phosphate buffer and a solution of H_2O_2 by a spectrophotometric method and compared with the standard BHT. The absorbance value (230 nm) of the reaction mixture was recorded at 10 min intervals between 0 and 40 min. For each concentration, a blank sample was used for background subtraction and the corresponding absorbance value for **2a**–**2o** is given in Table 4. The compound containing a 5-iodo group (**2e**) exhibited maximum antioxidant potential after 40 min. Compounds **2d** and **2c** emerged as the second most active compounds among those tested, with an absorbance value of 71% and 70%, respectively. This observation was in agreement with the results obtained using the DPPH protocol (compare Table 3). However, the antioxidant properties of the compounds possessing N-Et (**2h**) and N-Bn (**2k**) and no substitution (**2a**) were poor, as evidenced by their low absorbance values. The other compounds screened in this study exhibited inhibition that was comparable with the standard, BHT.

4. Conclusions

In summary, we prepared of 3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one derivatives in excellent yields as single diastereoisomers (*syn*-selectivity) through the chloroauric acid catalyzed aldolization between isatins and creatinine under aqueous conditions. The reaction was facile, high-yielding, and did not require solvent extraction and column chromatography. The radical scavenging activity of the prepared 3-hydroxyisatin derivatives revealed that compounds possessing halo groups at the C5-carbon (**2c**, **2d** and **2c**) exhibited comparable antioxidant potency to the standard. Furthermore, we applied our reaction conditions to a tandem reaction between isatin, creatinine and malononitrile. In this case, the products were obtained in excellent yield with complete *anti*-selectivity. Further studies aimed towards the preparation of more complex systems as well as kinetic studies to investigate the reaction mechanism are currently underway in our laboratory and will be reported in due course.

Acknowledgments

K. P thanks the Central Council for Research in Siddha (CCRS), India and T. P thanks the management of Inogent Laboratories Ltd., India. C. P. is grateful to the Science and Engineering Research Board (SERB) for the financial support (SERB/F/5666/2015-16).

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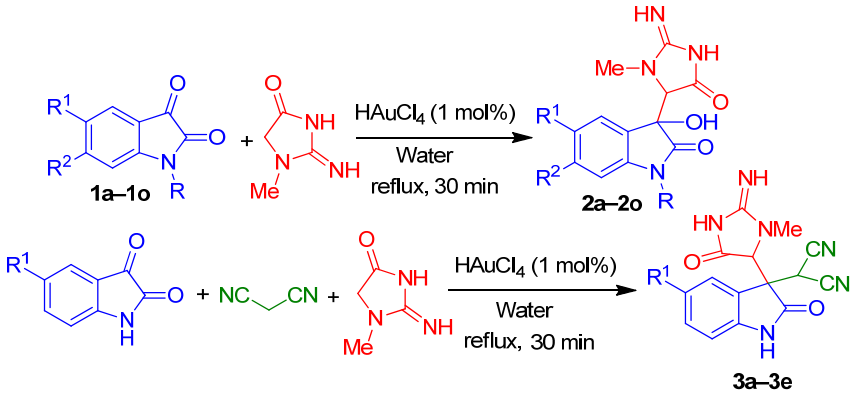
Graphical Abstract

Chin. J. Catal., 2017, 38: 775–783 doi: 10.1016/S1872-2067(17)62812-2

Gold-catalyzed addition reaction between creatinine and isatin: A sustainable and green chemistry approach for the diastereoselective synthesis of 3-substituted-3-hydroxyisatins

K. Parthasarathy, T. Ponpandian, C. Praveen *
Siddha Central Research Institute, Central Council for Research in Siddha (CCRS), India; Inogent Laboratories Private Limited, India; CSIR-Central Electrochemical Research Institute (CSIR-CECRI), India



Aldolization and three component condensation of isatin derivatives with creatinine under the catalysis of auric acid in water has been developed. The synthesized compounds exhibited moderate radical scavenging activity.

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金催化肌酸酐与靛红的加成反应：一种可持续的绿色方法用于非对映选择合成3-取代的3-羟基靛红

K. Parthasarathy [a], T. Ponpandian [b], C. Praveen [c,*]

[a] 悉达中央研究委员会 悉达中央研究所化学系, Arumbakkam, 金奈600106, 泰米尔纳德邦, 印度
[b] 工业发展区私人有限实验室, 海得拉巴500076, 特伦甘纳邦, 印度
[c] 中央电化学研究所功能材料部科学和工业研究理事会, 卡拉库迪600006, 泰米尔纳德邦, 印度

摘要: 报道了水介质中金催化肌酸酐与不同靛红之间的醛醇缩合反应. 该法无需繁杂的溶剂萃取和柱色谱技术, 只需简单的过滤即可将产物分离出来, 因而操作简单. 通过较宽范围的靛红衍生物的反应, 均可高产率并完全地制取相应的顺式醛醇缩合产物, 因此该法表现出较高的通用性. 还将该合成策略进一步拓展至靛红, 肌酸酐和丙二腈的串联反应, 可高产率、完全的制取反式多组分产物. 采用分光光度法测定了合成产物的抗氧化性能, 结果表明, 与标准物相比,含有卤素原子的三个化合物(**2c**, **2d**和**2e**)表现出最高的活性.

关键词: 肌酸酐; 金催化; 绿色化学; 非对映立体选择性; 抗氧化剂

收稿日期: 2017-01-05. 接受日期: 2017-02-28. 出版日期: 2017-05-05.

*通讯联系人. 电话: +91-9677733808; 电子信箱: chandrasekar.praveen@gmail.com

本文的英文电子版由Elsevier出版社在ScienceDirect上出版(http://www.sciencedirect.com/science/journal/18722067).