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Indium/Fe(III) - mediated regioselective *β*-cross-coupling aldol type addition reaction of activated alkenes with isatins/isatinimines in aqueous media

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Abstract. A highly efficient and regioselective *β*-cross coupling aldol type addition reaction of activated alkenes with isatin/isatinimine derivatives in the presence of Indium/Fe(III) in THF/H$_2$O at room temperature has described. Our synthetic protocol explores broad substrate scope and smoothly proceeds under base-free conditions. The resulting products are obtained in short reaction time with moderate to high yields. This is the first example of Mannich-type coupling of isatinimines with activated alkenes to afford the alkyl 3-(2-oxo-3-(phenylamino)indolin-3-yl)propanoates and 3-(3-oxoalkyl)-3-(phenylamino)indolin-2-ones.

Functionalized oxindoles bearing a 3,3′-disubstituted with a hetero atom at the C_3-position is a privileged structural motifs that exist in a large family of a bioactive natural products and a series of pharmaceutically active compounds.[1] Among them, 3-amino and 3-hydroxy oxindole frameworks have been present in a huge number of naturally occurring alkaloids and medicinally significant compounds.[2] For example, CRTH2 antagonist with good oral bioavailability,[3a] SSR-149415 which is used for the treatment of anxiety and depression.[3b] In addition to this, convolutamydines,[4a,b] 3-hydroxyglucoisatisin,[4c,d] celogentin K[4e,f] and dioxibrassinin[4g] are representative examples of biologically active 3-substituted-3-hydroxy oxindoles (Figure 1).

Inspired by these important scaffolds, a variety of synthetic methods have been developed for the synthesis of 3-substituted 3-hydoxy/amino oxindoles. For example, organo catalysed aldol reactions,[5] arylation of isatins[6] and direct hydroxylation of 3-alkyl-substituted oxindoles,[7] nucliophilic addition to imines,[8] alkylation of 3-amino oxindoles[9], Mannich reaction[10]. However, to the best our knowledge only a single example, Cheng and co-workers has been reported the *β* -reductive aldol coupling reaction of isatin derivatives with electron-deficient alkenes.[11] But this reaction requires longer reaction time and the use of ammonia gas cause inconvenience. Moreover, the substrate scope was also limited. In this regard it is desirable to develop efficient, convenient and practical method for the synthesis of 3-substituted 3-substituted-3-hydroxy/amino oxindole structural motifs.

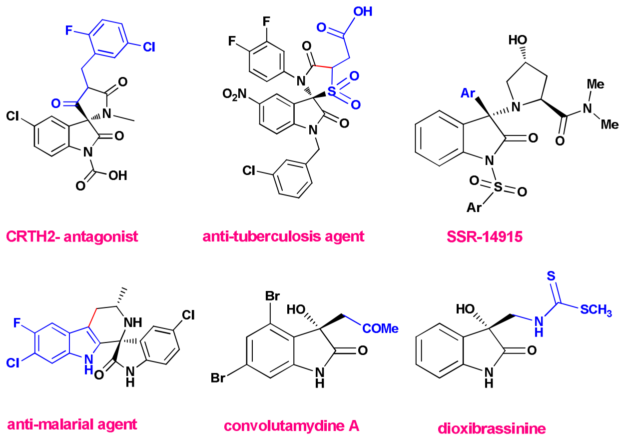

Figure 1. Some examples of biologically active quaternary 3-amino/hydroxyl oxindoles.

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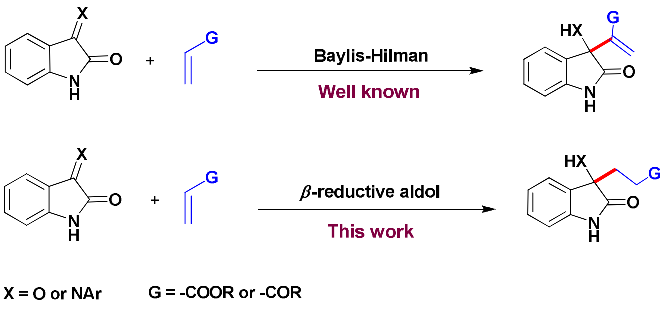
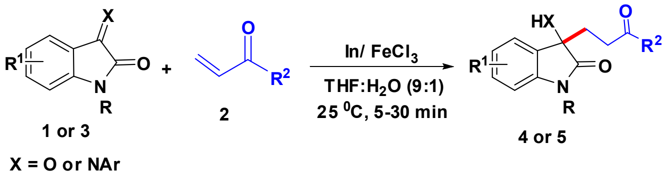


Scheme 1. The reactions of isatin with activated alkenes.

The Baylis–Hillman reaction is a significant carbon–carbon bond-forming reaction.[12] It involves the coupling of an activated alkene with isatin and results in Baylis–Hillman adduct With respect to development of a coupling reaction, the regioselective *β*-cross-coupling reaction is an attractive because it provides easy access for the synthesis of a variety of oxindole derivatives (Scheme 1).

Indium, by virtue of its unique properties, has emerged as a powerful metal to mediate organic reactions in aqueous media.[13] Indium metal is water or air – tolerant and in contrast to zinc it does not require any prior-to-use activation. Moreover, it can be handled safely without any apparent toxicity. In addition, Indium has a very low first ionization energy compared to zinc, accordingly it could be a potential reducing agent.[14]

In continuation of our efforts in the synthesis of 3- substituted oxindoles,[15] herein we report an efficient *β*-reductive aldol type addition of activated alkenes with isatin and isatinimines using In/$FeCl_3$ in aqueous media (Scheme 2). In this method, we synthesized a range of 3-substituted-3-hydroxy/amino oxindoles through the regioselective *β*-cross-coupling aldol type addition.

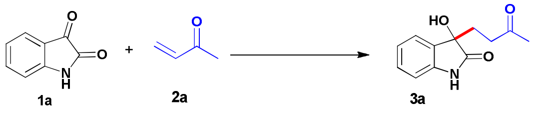


Scheme 2. In/$FeCl_3$-mediated regioselective ene-carbonyl cross coupling.

Results and discussions:

Our initial studies focused on the effect of different metallic co-reductants and solvents for the regioselective *β*-cross-coupling aldol type addition reaction of isatin **1a** and methyl vinyl ketone (MVK) **2a** at 25 °C and the results are depicted in Table 1. As shown in Table 1, a sequence of metals, such as Mo, Al, Mg, Fe, Sn and In were tested for the reaction. Among them In was found the most suitable metal for this coupling reaction (Table 1, entries 1-7 and 14-16). In order to improve the yield of the product, several lewis acids were screened as promoters (Table 1, entries 8-13) and it was observed that the $FeCl_3$ provided impressive improvement in yield (Table 1, entry 18). It is noteworthy to mention that the reaction did not proceeded either with alone metal or lewis acid (Table 1, entries 1-3 and 24). However, the use of combination of metal and lewis acid gave desired product. Later, solvent effect was also investigated for this method and it was revealed that the media had a remarkable effect and significant enhancement of the reaction was observed by the addition of water to THF. Among the different tested solvent systems THF:H_2O (9:1) was found to be an effective system in terms of yields (Table 1) and other solvent systems were found to be inefficient (Table 1, entries 19, 20and 22 and 23). By increasing the time of the reaction did not lead to any further improvements in the yield (Table 1, entry 17).

Table 1. Optimization of reaction conditions for the regioseletive ene-carbonyl coupling[a]



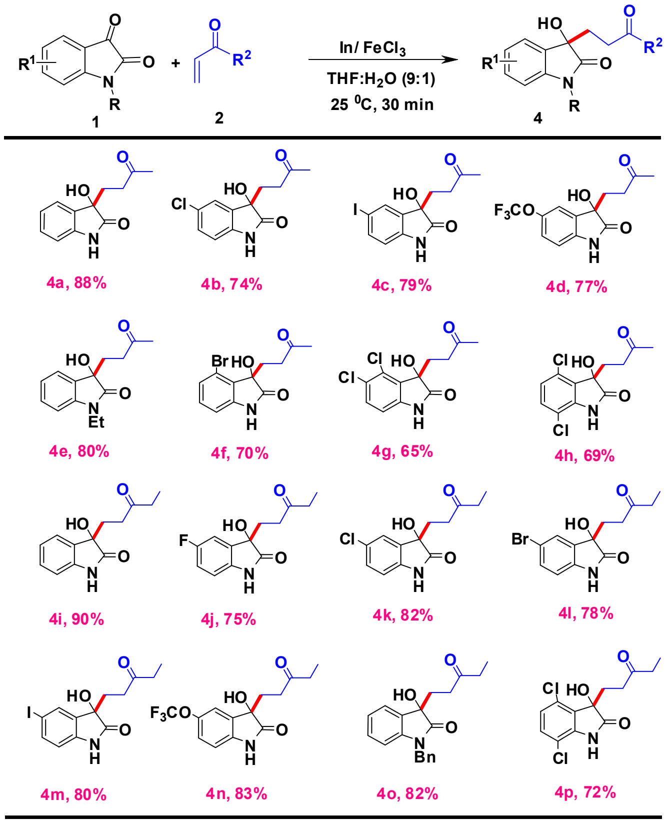
entry	metal	catalyst	solvent	time (h)	yield (%)[b]
1	Mo	-	THF:H_2O (9:1)	24	no reaction
2	Al	-	THF:H_2O (9:1)	24	no reaction
3	Fe	-	THF:H_2O (9:1)	24	no reaction
4	Sn	$Ni(OAc)_2.4H_2O$	THF:H_2O (9:1)	24	10
5	Fe	$InCl_3$	THF:H_2O (9:1)	24	15
6	Fe	$ZrCl_4$	THF:H_2O (9:1)	12	55
7	In	$ZnCl_2$	THF:H_2O (9:1)	10	65
8	In	$CuCl_2.2H_2O$	THF:H_2O (9:1)	24	15
9	In	$Bi(OTf)_3$	THF:H_2O (9:1)	24	5
10	In	$SnCl_2.2H_2O$	THF:H_2O (9:1)	10	50
11	In	$Sc(OTf)_3$	THF:H_2O (9:1)	20	5
12	In	$InCl_3$	THF:H_2O (9:1)	24	15
13	In	$Ni(OAc)_2.4H_2O$	THF:H_2O (9:1)	24	25
14	Mg	$FeCl_3$	THF:H_2O (9:1)	20	10
15	Sn	$FeCl_3$	THF:H_2O (9:1)	15	40
16	Fe	$FeCl_3$	THF:H_2O (9:1)	24	15
17	In	$FeCl_3$	THF:H_2O (9:1)	24	88
18	**In**	**$FeCl_3$**	**THF:H_2O (9:1)**	**0.5**	**88**
19	In	$FeCl_3$	DCM:H_2O (9:1)	1	5
20	In	$FeCl_3$	MeCN:H_2O(9:1)	0.5	50
21	In	$FeCl_3$	THF:H_2O (1:1)	1	50
22	In	$FeCl_3$	THF	1	20
23	In	$FeCl_3$	H_2O	24	no reaction
24	-	$FeCl_3$	THF:H_2O (9:1)	24	no reaction
25	In	-	THF:H_2O (9:1)	24	no reaction

[a] Reaction conditions: isatin **1a** (1 mmol), methyl vinyl ketone **2a** (1.2 mmol), metal (2 mmol), catalyst (5 mol%) in 5 mL of solvent at 25 ºC.

[b] Isolated yield.

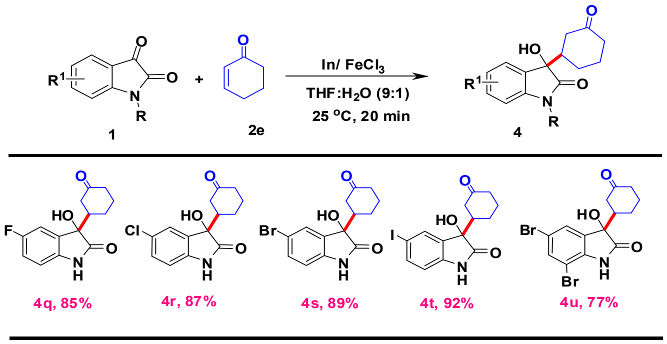
After achieving the optimized reaction conditions, the scope of aliphaitic enones and isatins were explored (Scheme 3). The reaction of methyl vinyl ketone (MVK) **2a** and ethyl vinyl ketone (EVK) **2b** with simple isatin gave corresponding products in high yields (Table 2, **4a** and **4i**). Isatins bearing different substituents on the nitrogen atom and on the aromatic ring could also be coupled effectively under this condition. For example 5-halo isatins reacted with **2a**/**2b** and resulted into moderate yields of coupling adducts (Table 2, **4b**, **4c** and **4j**- **4m**). Other 5-substituted (-OCF_3) isatins reacted smoothly with MVK and EVK to furnish desired product in high yield (Table 2, **4d** and **4n**). Similarly 4-substituted, 4,5-disubstituted and 4,7-disubstituted also afforded comparatively less yield of desired products (Table 2, **4f**-**4h** and **4p**). The substituents on nitrogen atom were found to have no effect on the reactivity (Table 2, **4e** and **4o**).

Table 2. Scope of regioselective *β*-reductive coupling of aliphatic enones with isatins[a,b]



[a] Reaction conditions: isatin 1 (1 mmol), aliphatic enones 2 (1 mmol), Indium (2 mmol), and $FeCl_3$ (5 mmol %) in 5 mL of $THF:H_2O$ (9:1) at 25 °C. [b] Isolated yield.

Table 3. Scope of regioselective *β*-reductive coupling of cyclic-enone with isatins.[a]



[a] Reaction conditions: isatins 1 (1 mmol), cyclohexenone 2c (1 mmol), Indium (2 mmol), and $FeCl_3$ (5 mmol%) in 5 mL of $THF:H_2O$ (9:1) at 25 °C. [b] Isolated yield.

Then we extended this method for the cyclic enone to different substituted isatins which gave good yields of the products (Table 3). For example, 5-halogenated isatins were reacted with cyclohex-2-ene-1-one in an identical condition and resulted in the expected products in high yields (Table 3, **4q-4t**).

The structure of one of the products, **4l** was confirmed by a single-crystal X-ray diffraction analysis (Figure 2). Compound **4d** was further confirmed by nmr studies (DEPT Experiment, See Supp. Info.). From the obtained yields of all the products, we observed the reactivity profile of α,β -unsaturated ketones is as following cyclohex-2-ene-1-one > EVK > MVK.

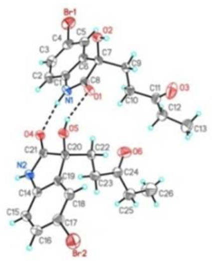
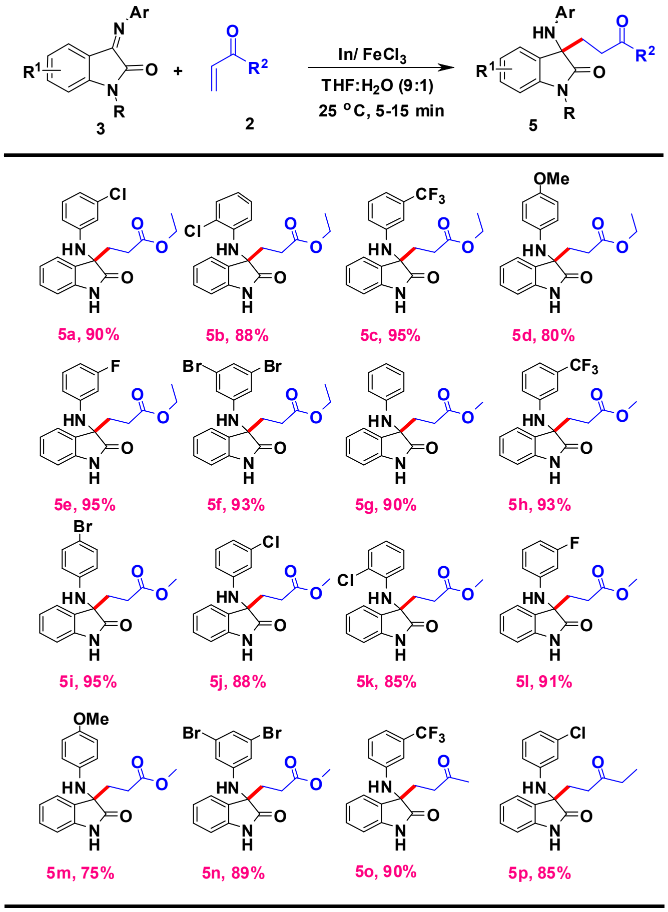


Figure 2. ORTEP diagram of the single-crystal X-ray structure of compound **4l**.

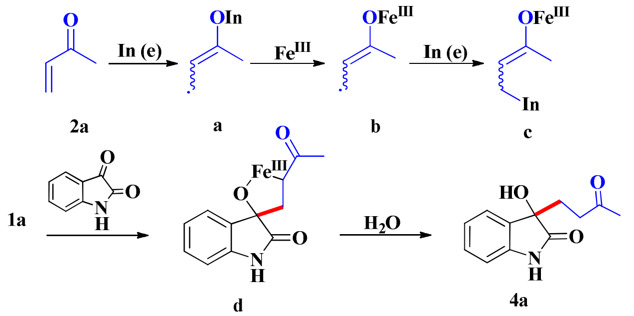
Table 4. Scope of regioselective *β*-reductive coupling of acrylates and aliphatic enones with isatinimines[a,b]



[a] Reaction conditions: isatinimines 3 (1 mmol), acrylates or aliphatic enones 2 (1 mmol), Indium (2 mmol), and $FeCl_3$ (5 mmol %) in 5 mL of $THF:H_2O$ (9:1) at 25 °C. [b] Isolated yield.

Encouraged by the results obtained from the regioselective β-cross-coupling aldol type addition reaction of isatins, then the scope of the present protocol was further extended by treating a different isatinimines with activated alkenes, such as **2a/2b** (methyl/ethyl vinyl ketone) and **2d/2e** (methyl/ethyl acrylate) under standard reaction conditions and the results are presented in table 4**.** Initially, the reaction of **2d** with 3-(phenylimino) indolin-2-one worked well to afford the desired product in high yield (Table 4**, 5g**). The imines containing substituents on phenyl group with either multifarious electronic property were successfully applied in this Mannich-type of coupling**.** For example, 3-(3-halophenylimino) indolin-2-ones were reacted efficiently with **2b, 2d** and **2e** to form the β -reductive Mannich products in good to high yields (Table 4, **5a**, **5e**, **5j**, **5l** and **5p**). Similarly 3-(3 (trifluoromethyl)phenylimino)indolin-2-one showed good reactivity with **2a, 2d** and **2e,** and furnished the resultant coupling products in high to excellent yields (Table 4, **5c**, **5h** and **5o**). In the same way 4-substituted and 3, 5-disubstituted imines also took part in this reaction with **2d** and **2e** to give the Mannich adducts in satisfactory yields (Table 4, **5d**, **5f**, **5i**, **5m** and **5n**).

A plausible mechanism is proposed based on previous reports[16] as shown in scheme **3**. The reaction is initiated by a single-electron transfer from Indium to the methyl vinyl ketone **2a** to form a radical enolate anion **a.** Brisk trapping of the oxygen-metal bond in the radical enolate anion **a** by $FeCl_3$ gives the γ-Fe(III)- substituted allylic radical **b**. The radical **b** is further reduced by Indium to furnish the corresponding allylic Indium species **c**. Finally, coupling of the γ-Fe(III)-substituted allylic Indium species **c** with an isatin results in the formation of **d** and followed by the hydrolysis of **d** would lead to the desired product **4a.**



Scheme 3. Putative mechanistic way for the formation of regioselective reductive aldol product **4a**.

We believe that the present method is amenable for the synthesis of novel compounds. In addition to this the method avoids the use of harsh and hazardous conditions.

Conclusion:

In summary, we have demonstrated a β–reductive aldol type addition of ativated alkenes with isatins/isatinimines promoted by In/$FeCl_3$ in aqueous media. This strategy is base free, atom-economical and regioselective for the synthesis of wide variety of 3-hydroxy/amino oxindole derivatives. Moreover, 3-amino oxindole derivatives had never synthesized before by β–reductive aldol type reaction.

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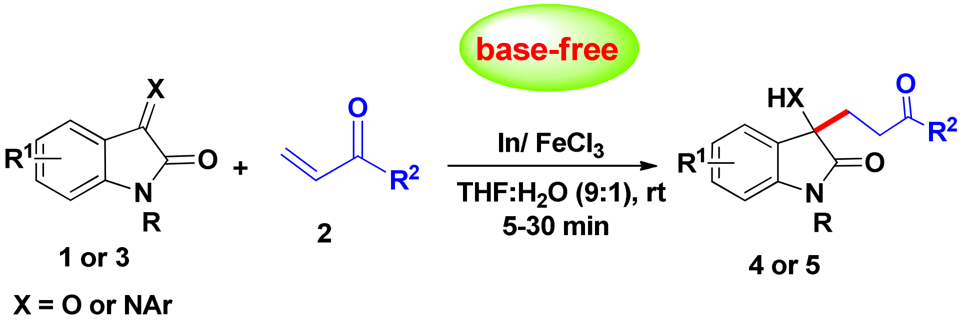

1 or 3

X = O or NAr

2

4 or 5