RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

RSCPublishing

COMMUNICATION

www.rsc.org/

Ru(III) –catalyzed α-cross-coupling aldol type addition reaction of activated olefins with isatins

A. Sanjeeva Kumar[a], Palakuri Ramesh[a], G. Santosh Kumar[a], A. Swetha[a], Jagadeesh Babu Nanubolu [b] and H. M. Meshram[a]*

Abstract. A α-cross-coupling aldol type addition reaction activated olefins with isatins has been described in presence of ruthenium (III) chloride and tributyltin hydride (TBTH) at room temperature. This method is found to work consistently for the delivering of ene-carbonyl coupled products in good to excellent yields with moderate to acceptable selectivity. The substrate scope of the present method was briefly discussed.

The reductive aldol reaction has received considerable attention in the C-C bond formation because it does not require the pre-activation of nucleophile and this process allows the coupling of a two π –partners in a one pot.[1] Various catalysts have been used for the reductive aldol coupling such as, rhodium,[2] cobalt,[3] iridium,[4] ruthenium,[5] palladium,[6] copper[7] and nickel.[8] On the other hand, 3-substituted-3-hydroxy-2-oxindole entities are found in a large number of naturally occurring alkaloids with different biological activities such as potent anticancer, anti-HIV, antioxidant and neuroprotective properties.[9] Selective representative examples are convolutamydines,[10a] donaxaridines,[10b,c] maremycins,[10d] dioxibrassinines,[10e] celogentin K,[10f] 3-hydroxy hydroxyglucoisatisins,[10g] and TMC-95A[10h] (Fig 1). Because of their structural significance in biological sciences, a number of strategies have been developed for the synthesis of such structural motifs, which includes allylation of isatins,[11] nucleophilic addition to isatins,[12] and direct hydroxylation of 3-substituted oxindoles.[13] Though the synthesis of 3-substituted oxindoles is reported, the synthesis of alkyl 2-(3-hydroxy-2-oxoindolin-3-yl)propanoates or 3-hydroxy-3-(3-alkyl)indolin-2-ones or 2-(3-hydroxy-2-oxoindolin-3-yl)propanenitriles remain unexplored. So, it is desirable to develop efficient and general method using readily available catalyst.

[a]*Medicinal Chemistry and Pharmacology Division,* [b]*Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India. E-mail:hmmeshram@yahoo.com; Tel.: +91-27191640, Fax: 91-40-27160512.*

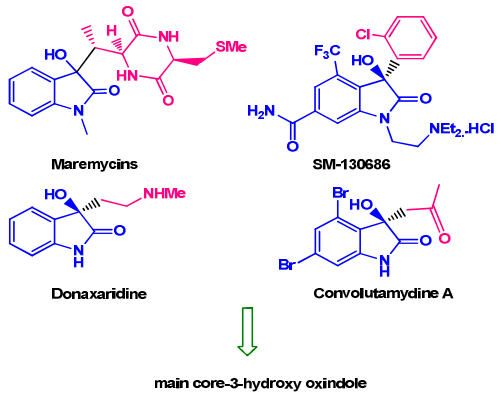
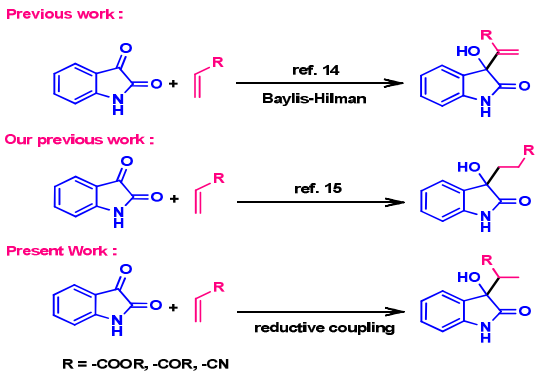


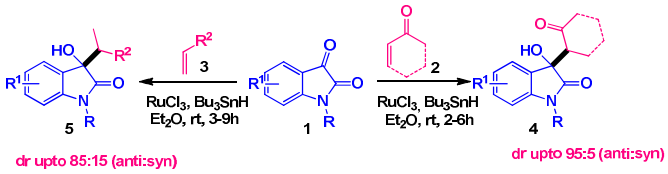
Figure 1. Some examples of biologically active quaternary 3-amino/hydroxyl oxindoles.

However, to the best of our knowledge this is the first example of reductive coupling of activated olefins with isatins for the synthesis of alkyl 2-(3-hydroxy-2-oxoindolin-3-yl)propanoate, 3-hydroxy-3-(3-alkyl)indolin-2-one and 2-(3-hydroxy-2-oxoindolin-3-yl)propanenitrile derivatives.



Scheme 1. The reactions of isatin with activated olefins.

Generally, the coupling reaction between activated olefins with an isatin in the presence of a base gives the Baylis–Hillman[14] type products in which a C-C bond was formed between the α-carbon atom of the activated olefin and the C_3-carbon atom of the indoline-2,3-dione. In our previous communication, we have endeavored *β*-cross coupling aldol type addition reaction of activated olefins with isatins/isatinimines in presence of In/Fe(III) catalytic system.[15] Based on our continuing interest in the synthesis of 3-substituted-3-hydroxy-2-oxindole,[16] herein we would like to disclose the *α*-cross-coupling aldol type addition reaction of range of activated olefins (methyl vinyl ketone, methyl/ethyl acrylates, acrylonitrile and cyclohexenone) with isatins to afford the valuable 3-funtionalized-3-hydroxy oxindoles in a single step by using $RuCl_3$/TBTH catalytic system at room temperature.



Scheme 2. $RuCl_3$ - catalyzed reductive ene-carbonyl coupling.

Results and discussions:

To find out the reaction conditions, our initial investigations were focused on the reductive ene-carbonyl coupling of methyl vinyl ketone **2a** (1.2 mmol) with an isatin **1** (1 mmol) using TBTH as hydrogen source (1.5 mmol) at room temperature and the results are summarized in table 1. Initially, different metal catalysts were tested for this transformation and it was found that the $RuCl_3$ is the most effective catalyst for driving the reaction to achieve the product in high yield as a mixture of diastereomers with 95:5 selectivity (Table 1, entry 6). The diastereomeric ratio of the resultant product was analyzed by the ^{1}HNMR of the crude product. Whereas other tested metal catalysts were led to poor results (Table 1, entries1-5 and 11-14) and no reaction was observed in the absence of metal catalyst (Table 1, entry 7). It indicates that the importance of the metal catalyst in the present method. With the $RuCl_3$ as optimal catalyst, we next investigated the influence of the solvents. Among the different screened solvents, the best result was achieved when the reaction was performed in diethyl ether (Table 1, entry 6) and other solvents were showed poor results (Table 1, entries 9 and 10). To further optimize the reaction conditions, we were decided to investigate the effect of catalyst loading. Finally, the excellent result was obtained with 5 mol% of the catalyst ($RuCl_3$) (Table 1, entry 6). When the catalyst ($RuCl_3$) loading was decreased to 2 mol%, the product **4a** was formed in lower yield (Table 1, entry 8). The structure of the expected reductive aldol product **4a** was confirmed by spectroscopic data (^{1}H, ^{13}C, DEPT, IR and Mass).

By employing the optimal reaction conditions, we were keen to examine the generality of this reaction by treating a variety of isatins with enones (methyl vinyl ketone/cylohexenone **2a**/**2b**) and the results are depicted in table 2&3. Initially, the ene-carbonyl coupling reaction of **2a** and **2b** with simple isatin **1** underwent smoothly and resulted into expected product as inseparable diastereomeric mixture with high yield (Table 3, **4a** and **4l**). Isatins bearing substituents with diverse electronic properties at the 5th position were successfully coupled with **2a** and **2b** in the present protocol. For example, the reaction of 5-halo isatins proceeded smoothly and afforded corresponding products in high yields with the variable selectivity (Table 2&3**, 4b-4e** and **4m-4p**). Other 5-substitued isatins were also showed fine reactivities and furnished the aldol products in high yields with poor to good selectivity (Table 2&3**, 4f, 4g** and **4q, 4r).** In addition to this, 4-substituted, 4,6- disubstituted, 4,7-disubstituted and 5,7- disubstituted isatins were also participated in this reaction with **2a**/**2b** and gave comparatively with moderate yields of the products (Table 2&3, **4i-4k** and **4s-4u**). Furthermore, *N*-protected isatins were also successfully cross-coupled with **2a**/**2b** to offer the corresponding products in acceptable yields (Table 2&3, **4h** and **4v-4x**).

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

1 2a 4a

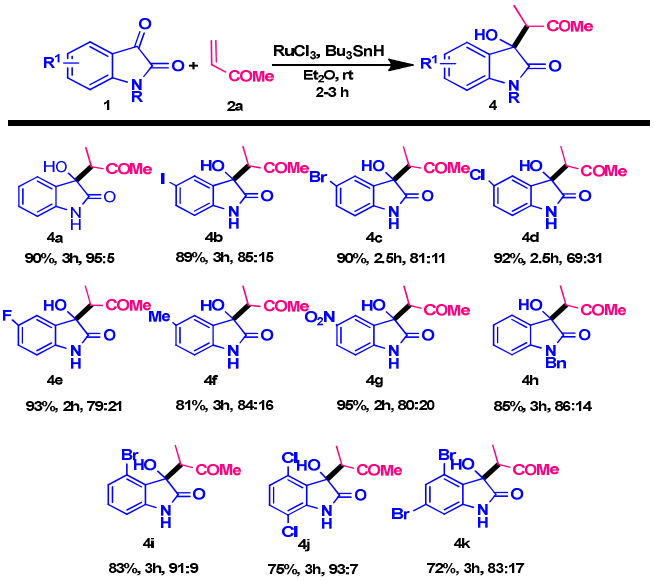
Entry	catalyst (mol%)	Solvent	Time	Yield (%)[b]	dr (anti;syn)[c]
1	CuCl (5)	Et_2O	10h	65	60:40
2	$Ni(acac)_2$ (5)	Et_2O	20h	35	52:48
3	$Cu(OAc)_2.H_2O$ (5)	Et_2O	20h	20	55:45
4	$FeCl_3$ (5)	Et_2O	30h	25	53:47
5	$InCl_3$	Et_2O	24h	10	55:45
6	$RuCl_3$ (5)	Et_2O	3h	90	95:5
7	-	Et_2O	24h	no reaction	-
8	$RuCl_3$ (2)	Et_2O	10h	45	95:5
9	$RuCl_3$ (5)	$PhCH_3$	24h	30	80:20
10	$RuCl_3$ (5)	C_6H_6	10h	60	85:15
11	$CoCl_2$ (2)	Et_2O	20h	40	56:44
12	$ZrCl_4$ (5)	Et_2O	24h	25	68:32
13	$Fe(acac)_3$ (5)	Et_2O	24h	30	55:45
14	$NiCl_2$ (5)	Et_2O	24h	40	51:49

Reaction conditions: isatin **1a** (1 mmol), methyl vinyl ketone **2a** (1.2 mmol), catalyst (X mol%) and TBTH (1.5 mmol) in 5 mL of solvent at room temperature. [b] Isolated yield. [c] Diastereomeric ratio.

The scope of this method was further supported by examining a methyl/ethyl acrylates **3a**/**3b** in place of enones and the results are presented in table 4. At first, the simple isatin underwent the reductive coupling reaction with **3a**/**3b** and provided an ene-carbonyl coupled product in high yield with poor selectivity (Table 4, **5a** and **5l**). It was found that a range of isatins were reacted in an efficient manner with **3a**/**3b** under the optimized reaction conditions. For example, the 5-halo isatins were took place smoothly and afforded the corresponding products in high yields nearly with the same selectivity (Table 4**, 5b-5d** and **5p, 5q**). In addition to simple and 5-substituted isatins, 4,6- disubstituted and various N-substituted

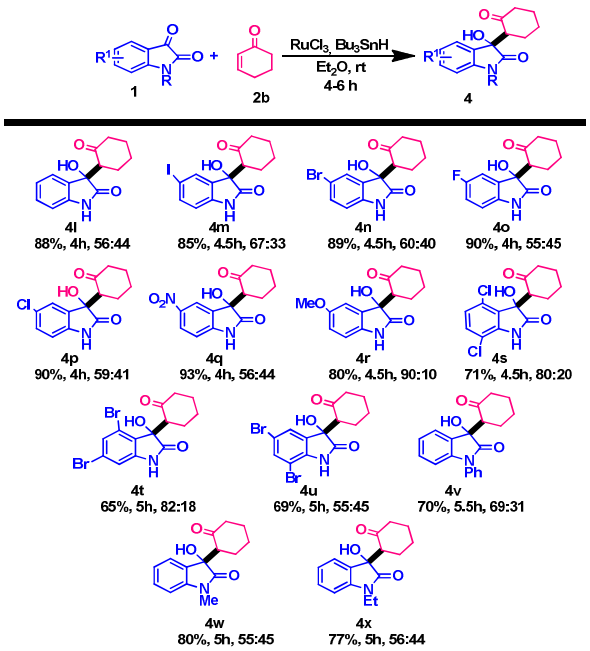
isatins were also coupled with **3a**/**3b** to produce the cross-coupled products in moderate to good yields (Table 4, **5e-5k** and **5m-5o**).

Table 2. Scope of reductive ene-carbonyl coupling of methyl vinyl ketone with isatins[a]



[a] Reaction conditions: isatin **1** (1 mmol), methyl vinyl ketone **2a** (1.2 mmol), $RuCl_3$ (5 mmol %) and TBTH (1.5 mmol) in 5 mL of Et_2O at room temperature. [b] Isolated yield. [c] Diastereomeric ratio.

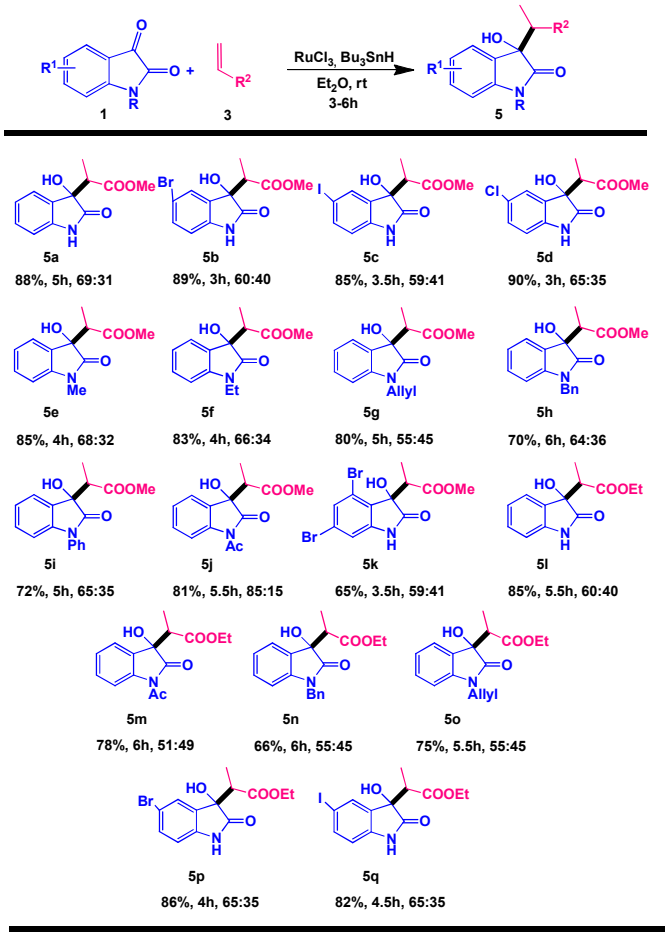
Table 3. Scope of reductive ene-carbonyl coupling of cyclohexenone with isatins[a]



[a] Reaction conditions: isatin **1** (1 mmol), cyclohexenone **2b** (1.2 mmol), $RuCl_3$ (5 mmol %) and TBTH (1.5 mmol) in 5 mL of Et_2O at room temperature. [b] Isolated yield. [c] Diastereomeric ratio.

Inspired by the above achievement from the reductive ene-carbonyl coupling of enones and acrylates with isatin, we then turned our attention to apply this method to acrylonitrile **3c** and the results are depicted in table 5. As shown in table 5, it was found that a variety of isatins were reacted well with coupling partner **3c** under the standard reaction conditions. For example, simple isatin smoothly participated in the reductive ene-carbonyl coupling reaction and gave the coupled product in good yield with moderate selectivity (Table 5, **5r**). Other isatins like 5-F, 5-Br and 5-I isatins also furnished the aldol adducts in acceptable yields (Table 5, **5s-5u**).

Table 4. Scope of reductive ene-carbonyl coupling of methyl/ethyl acrylates with isatins[a]



[a] Reaction conditions: isatin **1** (1 mmol), methyl/ethyl acrylate **3** (1.2 mmol), $RuCl_3$ (5 mmol %) and TBTH (1.5 mmol) in 5 mL of Et_2O at room temperature. [b] Isolated yield. [c] Diastereomeric ratio.

We have proposed the reaction mechanism for reductive ene-carbonyl coupling reaction based on previous reports[17] (Scheme 3). Initially, TBTH reacts with $RuCl_3$ and gave the ruthenium hydride complex **a**. The 1, 4-addition of ruthenium hydride species to methyl vinyl ketone **2a** gives the ruthenium enolate **b**. Next, the aldol addition reaction of ruthenium enolate to an isatin offers a (2-oxo-3-(3-oxobutan-2-yl) indolin-3 yloxy) ruthenium (III) chloride **c** and is followed by transmetallation with TBTH, results in the formation of a 3-(3-oxobutan-2-yl)-3-(tributylstannyloxy) indolin-2-one **d**. Finally the quenching of the **d** with aq.NH_4Cl produces reductive coupling

product **4a**. We have observed that the generation of metal-hydride species is essential for this method.

The structure of one of the products **4r** was further confirmed by a single-crystal X-ray diffraction analysis (Figure 2). Based on the single-crystal structure we have identified major isomer as anti.

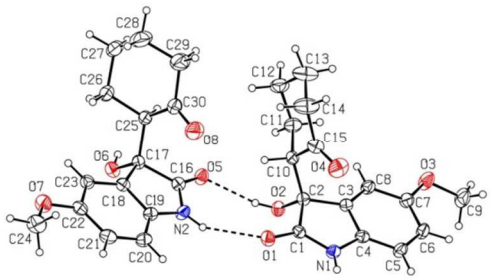
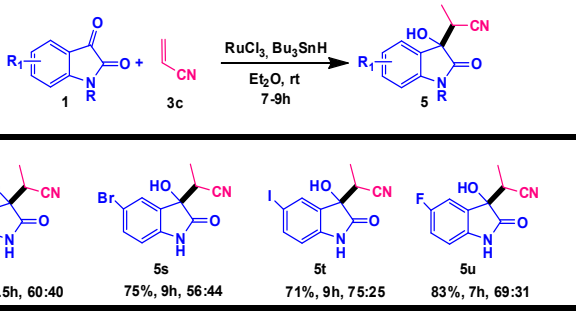
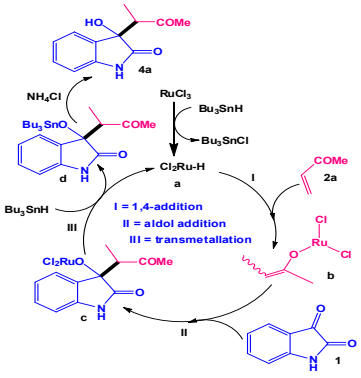


Figure 2. ORTEP diagram of the single-crystal X-ray structure of compound **4r**.

Table 5. Scope of reductive ene-carbonyl coupling of acrylonitrile with isatins[a]



[a] Reaction conditions: isatin 1 (1 mmol), acrylonitrile 3c (1.2 mmol), $RuCl_3$ (5 mmol %) and TBTH (1.5 mmol) in 5 mL of Et_2O at room temperature. [b] Isolated yield. [c] Diastereomeric ratio.



Scheme 3. Plausible mechanistic pathway for the reductive ene-carbonyl coupling.

Conclusion:

In summary, we have established the ruthenium (III) catalyzed an efficient α-cross-coupling aldol type addition reaction of activated olefins with isatins by using TBTH at room temperature. Our strategy has proven to be quite general, atom-economical and provides easy access for the synthesis of a wide variety of 3-functionalized-3-hydroxy oxindoles. Biological evaluations of our synthetic molecules are currently under progress in our lab.

Acknowledgment

A. S. K., P. R., G. S. K., and A. S. thank the CSIR-UGC India for award of a fellowship and Dr. A. Kamal, Outstanding scientist and Head of MCP Division, for his support and encouragement.

The authors thank CSIR- India for financial support as part of XII five year plan programme under title ORIGIN CSC 0108.

References

1. a) H.-Y. Jang, R. R. Huddleston and M. J. Krische, *Chemtracts*, 2003, **16**, 554; (b) H.-Y. Jang and M. J. Krische, *Eur. J. Org. Chem*., 2004, **19**, 3953; (c) H.-Y. Jang and M. J. Krische, *Acc. Chem. Res*., 2004, **37**, 653; (d) P. Chiu, *Synthesis*, 2004, 2210; (e) M.-Y. Ngai, J.-R. Kong, and M. J. Krische, *J. Org. Chem*., 2007, **72**, 1063.
2. (a) A. Revis and T. K. Hilty, *Tetrahedron Lett*., 1987, **28**, 4809; (b) I. Matsuda, K. Takahashi and S. Sato, *Tetrahedron Lett*., 1990, **31**, 5331; (c) S. J. Taylor, and J. P. Morken, *J. Am. Chem. Soc*., 1999, **121**, 12202; (d) C.-X. Zhao, J. Bass and J. P. Morken, *Org. Lett*., 2001, **3**, 2839; (e) S. J. Taylor, M. O. Duffey and J. P. Morken, *J. Am. Chem. Soc*., 2000, **122**, 4528.
3. (a) T. G. Baik, A. L. Luis, L. C. Wang and M. J. Krische, *J. Am. Chem. Soc*., 2001, **123**, 5112; (b) L. C. Wang, H.-Y. Jang, Y. Roh, V. Lynch, A. J. Schultz, X. Wang and M. J. Krische, *J. Am. Chem. Soc*., 2002, **124**, 9448; (c) H. W. Lam, P. M. Joensuu, G. J. Murray, E. A. F. Fordyce, O. Prieto and T. Luebbers, *Org. Lett*., 2006, **8**, 3729.
4. C. X. Zhao, M. O. Duffey, S. J. Taylor and J. P. Morken, *Org. Lett*., 2001, **3**, 1829.
5. T. Doi, T. Fukuyama, S. Minamino and I. Ryu, *Synlett*, 2006, **18**, 3013.
6. S. I. Kiyooka, A. Shimizu and S. Torii, *Tetrahedron Lett*., 1998, **39**, 5237.
7. (a) P. Chiu, B. Chen and K. F. Cheng, *Tetrahedron Lett*.,1998, **39**, 9229; (b) D. Zhao, K. Oisaki, M. Kanai and M. Shibasaki, Tetrahedron Lett., 2006, **47**, 1403; (c) O. Chuzel, J. Deschamp, C. Chausteur and O. Riant, *Org. Lett*., 2006, **26**, 5943.
8. C. C. Chrovian and J. Montgomery, *Org. Lett*., 2007, **3**, 537.
9. For reviews of oxindole alkaloids, see: (a) S. Peddibhotla, *Curr. Bioact. Compd*., 2009, **5**, 20. (b) C. V. Galliford and K. A. Scheidt, *Angew. Chem*., 2007, **119**, 8902; (c) K. Monde, K. Sasaki, A. Shirata and M. Tagusuki, *Phytochemistry*, 1991, **30**, 2915; (d) M. Suchy, P. Kutschy, K. Monde, H. Goto, N. Harada, M. Takasugi, M. Dzurilla and M. Balentova, *J. Org. Chem*., 2001, **66**, 3940; (e) T. Bui, S. Syed and C. F. Barbas, *J. Am. Chem. Soc*., 2009, **131**, 8758.
10. (a) Y. Kamano, H. P. Zhang, Y. Ichihara, H. Kizu, K. Komiyama and G. R. Pettit, *Tetrahedron Lett*., 1995, **36**, 2783; (b) H. B. Rasmussen and J. K. MacLeod, *J. Nat. Prod*., 1997, **60**, 1152; (c) T. Kawasaki, M. Nagaoka, T. Satoh, A. Okamoto, R. Ukon and A. Ogawa, *Tetrahedron*, 2004, **60**, 3493; (d) W. Balk-Bindseil, E. Helmke, H. Weyland and H. Laatsch, *Liebigs Ann*., 1995, 1291; (e) K. Monde, K. Sasaki, A. Shirata and M. Tagusuki, *Phytochemistry*, 1991, **30**, 2915;

(f) H. Suzuki, H. Morita, M. Shiro and J. Kobayashi, *Tetrahedron*, 2004, **60**, 2489; (g) A. Frechard, N. Fabre, C. Pean, S. Montaut, M. T. Fauvel, P. Rollin and I. Fouraste, *Tetrahedron Lett*., 2001, **42**, 9015; (h) J. Kohno, Y. Koguchi, M. Nishio, K. Nakao, M. Kuroda, R. Shimizu, T. Ohnuki and S. Komatsubara, *J. Org. Chem*., 2000, **65**, 990.

11. (a) X.-C. Qiao, S.-F. Zhu and Q.-L. Zho, Tetrahedron: Asymmetry, 2009, **20**, 1254; (b) T. M. Jared, V. H. Nadine, E. M. Maximillian, P. C. Stephen and T. S. Jared, *Org. Lett.*, 2013, **15**, 5615; (c) Z.-Y. Cao, Y. Zhang, C.-B. Ji, and J. Zhou, *Org. Lett.*, 2011, **13**, 6398; (d) A. Benito, A. Pedro and R.-A. Raquel, *J. Org. Chem.*, 2005, **70**, 3198.
12. (a) V. H. Nadine, C. T. Yng, T. T. Ngon and K. F. Annaliese, *Org. Lett.*, 2012, **14**, 2218; (b) Z. Y. Cao, Y. Zhang, C. B. Ji and J. Zhou, *Org. Lett.*, 2011, **13**, 6398; (c) X. C. Qiao, S. F. Zhu and Q. L. Zhou, *Tetra. Asymm.*, 2009, **20**, 1254; (d) N. V. Hanhan, A. H. Sahin, T. W. Chang, J. C. Fettinger and A. K. Franz, *Angew. Chem., Int. Ed*., 2010, **49**, 744; (e) J. Deng, S. Zhang, P. Ding, H. Jiang, W. Wang and J. Li, *Adv. Synth. Catal.*, 2010 , **352**, 833.
13. (a) D. Sano, K. Nagata and T. Itoh, *Org. Lett*., 2008, **10**, 1593; (b) T. Bui, N. R. Candeias, and C. F. III. Barbas, *J. Am. Chem. Soc.*, 2010, **132**, 5574; (c) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru and S. Kanemasa, *J. Am. Chem. Soc.*, 2006, **128**, 16488.
14. (a) F. Zhong, G.-Y. Chen and Y. Lu, *Org. Lett.*, 2011, **13**, 82; (b) Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang and J. Zhou, *J. Am. Chem. Soc*., 2010, **132**, 15176; (c) Y. M. Chung, Y. J. Im and J. N. Kim, *Bull. Korean Chem Soc*., 2002, **23**, 1651; (d) S. C. Kim, S. Gowrisankar and J. N. Kim, *Tetrahedron Lett*., 2006, **47**, 3463; (e) S. C. Kim, K. Y. Lee, S. Gowrisankar and J. N. Kim, *Bull. Korean Chem . Soc*., 2006, **27**, 1133.
15. A. S. Kumar, P. Ramesh, G. S. Kumar, J. B. Nanubolu, T. P. Rao and H. M. Meshram. *RSC. Adv*., 2015, **5**, 51581.
16. (a) H. M. Meshram, D. A. Kumar, P. R. Goud and B. C. Reddy, *Synth. Commun*., 2010**, 40**, 39; (b) H. M. Meshram, P. Ramesh, B. C. Reddy, B. Sridhar and J. S. Yadav, *Tetrahedron*, 2011, **67**, 3150; (c) H. M. Meshram, P. Ramesh, B. C. Reddy and G. S. Kumar, C*hem. Lett.*, 2011, **4**, 357; (d) H. M. Meshram, P. Ramesh, A. S. Kumar and A. Swetha, *Tetrahedron Lett.*, 2011, **52**, 5862; (e) H. M. Meshram, N. N. Rao, L. C. Rao and N. S. Kumar, *Tetrahedron Lett.*, 2012, **53**, 3963; (f) B. T. Pramod, K. Sirisha, A. V. S. Sarma, J. N. Babu and H. M. Meshram, *Tetrahedron*, 2013, **69**, 6415; (g) B. T. Pramod and H. M. Meshram, *RSC. Adv.*, 2014, **4**, 6019; (h) B. T. Pramod and H. M. Meshram, *RSC. Adv.*, 2014, **4**, 5343.
17. (a) E. Yamaguchi, J. Mowat, T. Luong, and M. J. Krische, *Angew. Chem. Int. Ed.*, 2013, **52**, 8428; (b) D. Zhao, K. Oisaki, M. Kanai and M. Shibasaki, *Tetrahedron Lett.*, 2006, **47**, 1403; (c) J. Joseph, F. Jaroschik, D. Harakat, K. V. Radhakrishnan, J. Vasse, and J. Szymoniak, *Chem. Eur. J.*, 2014, **20**, 5433; (d) K. Sato, M. Isoda, Y. Tokura, K. Omura, A. Tarui, M. Omote, I. Kumadaki and A. Ando, *Tetrahedron Lett.*, 2013, **54**, 5913.

Ru(III) –catalyzed *α*-cross-coupling aldol type addition reaction of activated olefins with isatins

A. Sanjeeva Kumar, G. Santosh Kumar, A. Swetha, Palakuri Ramesh and H. M. Meshram*