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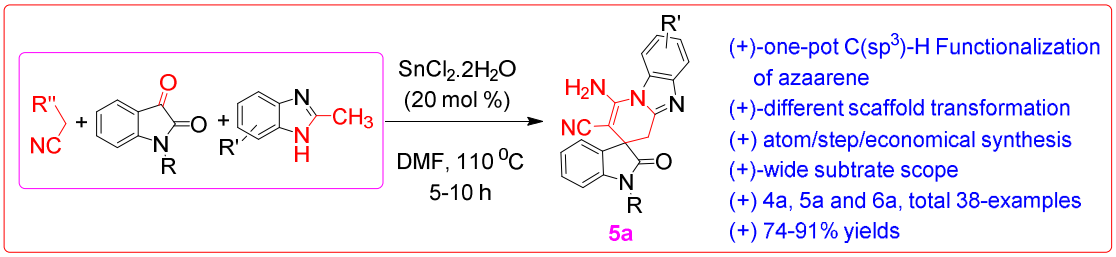

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A novel one-pot multi-component synthesis of 3, 3'disubstituted oxindoles and spirooxindoles scaffold via Sn-catalyzed C(sp3)-H functionalization of azaarenes by sequential Knoevenagel-Michael-Cyclization reaction†

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Sn-catalyzed C(sp3)-H bond functionalization of 2-methyl azaarenes/ 2-(azaaryl)methanes has been achieved first time in one-pot multi-component reaction with isatin, active methylene compounds via a Tandem sequential Knoevenagel-Michael-Intramolecular C-N Cyclization. This strategy provides cost effective new access to potent biologically/medicinally important spirooxindole/ 3,3'-disubstituted 2-oxindole in good to excellent yields.

The 3,3'-disubstituted 2-oxindoles and spirooxindoles[1] are key architectural motifs not only found in the various naturally occurring alkaloids/ natural products but also in biologically potent compounds such as gelsemine, oxogelsemine, alstonisine, spirotryprostatin-A (Figure 1).[2]

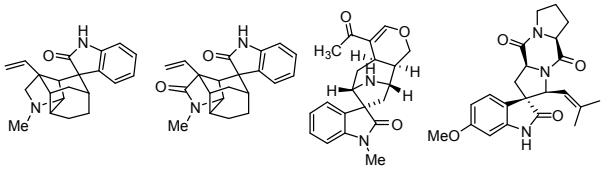
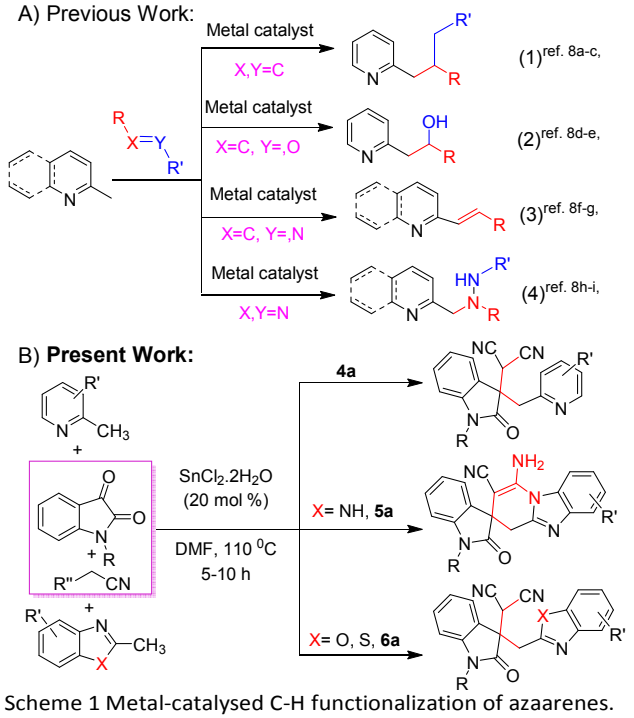


Figure 1 Bioactive compounds containing a spirooxindole framework.

Moreover, rich structural diversity and diverse chemical functionality of spirooxindoles and 3,3'-disubstituted 2-oxindoles are important for the synthesis of pharmacophore substances possessing wide spectrum biological activities[3] as well as one of the attractive scaffolds for the library design and drug discovery[4] since the biological activity varies with varying substituent's at C3 positions.



Scheme 1 Metal-catalysed C-H functionalization of azaarenes.

Due to potent pharmaceutical important in library design and drug discovery, various approaches for the synthesis of spirooxindoles[5] have been developed. However, synthesis of diverse functional molecules via C-H functionalization of prefunctiolized motifs is a straightforward, sustainable and convenient strategy, which has gained significant interest from academia and industry.[6] Hence, $Bi(OTf)_3$ catalyzed sp3 C-H bond functionalization of 2-alkyl azaarenes to isatylidene

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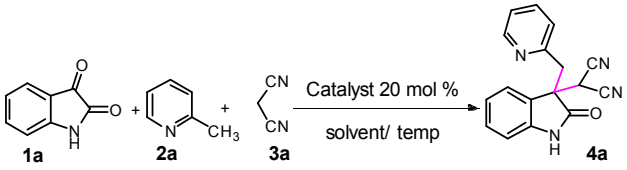
† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for compounds 4, 5 and 6, and copies of 1H and 13C NMR spectra, Single-crystal X-ray data of 4q (CCDC 1053586) and 5d (CCDC 1053587). See DOI: 10.1039/x0xx00000x

malononitriles[7] and metal catalyzed C-C and C-N bond formation via sp3 C-H functionalization of azaarenes have been well reported in the literature (Previous work Scheme 1).[8] Even though the 3,3'-disubstituted 2-oxindoles and spirooxindoles are promising key motifs in biologically potent compounds, surprisingly multi-component reaction (MCR) strategies via sp3 C-H functionalization of azaarenes has been a quite rarely explored.[9] Therefore, development of practical, cost-effective and atom economical new MCR versatile strategies for the synthesis of 3,3'-disubstituted 2-oxindoles and spirooxindoles via sp3 C-H functionalization of azaarenes is still challenging and remains in high demands. Encouraged by wider application of spirooxindoles/3,3'-disubstituted 2-oxindoles in life sciences, pharmaceuticals, pharmacophore and drug discovery and in continuation of our endeavour towards the development of one pot MCR protocols[10a,b] as well as C(sp3)-H functionalization of azaarenes.[10c] we envisioned a novel, efficient one pot multi-component protocol comprising a domino Knoevenagel-Michael-cyclization sequential tandem reaction via Sn-catalyzed C(sp3)-H functionalization of azaarenes with isatins and active methylene compounds to obtain a novel 3,3'-disubstituted 2-oxindoles and spirooxindoles scaffold (Present work, Schme1).

To test the feasibility of our hypothesis, initially, we began our studies by evaluating the reaction between isatin **1a,** 2-picoline **2a** and malononitrile **3a** using (20 mol %) $SnCl_2.2H_2O$ catalyst in 1,4-Dioxane solvent at 110 ^{0}C for 14 h and provided the desired product **4a** in 74% yield. Encouraged by the initial results, the screening of solvents, catalysts, as well as the influence of temperature, catalyst loading has been investigated to establish the optimized the reaction conditions (Table 1).

The results of a screening of solvents revealed that dimethylformamide shows the excellent performance in short reaction time compared to other solvents (entries 3-9), whereas neat reaction proceeds slowly at higher temperature that to a longer reaction time afforded **4a** in a lower yield (entry 2). Among the different catalysts screened (entries 10-15), F_3B-Ether and $SnCl_4$ catalyst afforded 4a in 77% and 62% yield, respectively (entry 10,11), however, $SnCl_2.2H_2O$ catalyst shows best performance (entry 7). The effect of reaction temperature was investigated; it was observed that the reaction performed at the 110 ^{0}C provided best results (entries 7, 16, 17). The effect of catalyst loading was examined, 20 mol % $SnCl_2.2H_2O$ catalysts provided the best performance compared 10 and 15 mol % (entries 7, 18, 19). The controlled experiment study reveals that in the absence of $SnCl_2.2H_2O$ catalyst, the formation of **4a** was not observed.

Table 1 Optimization of the Reaction Conditions.[a,b]



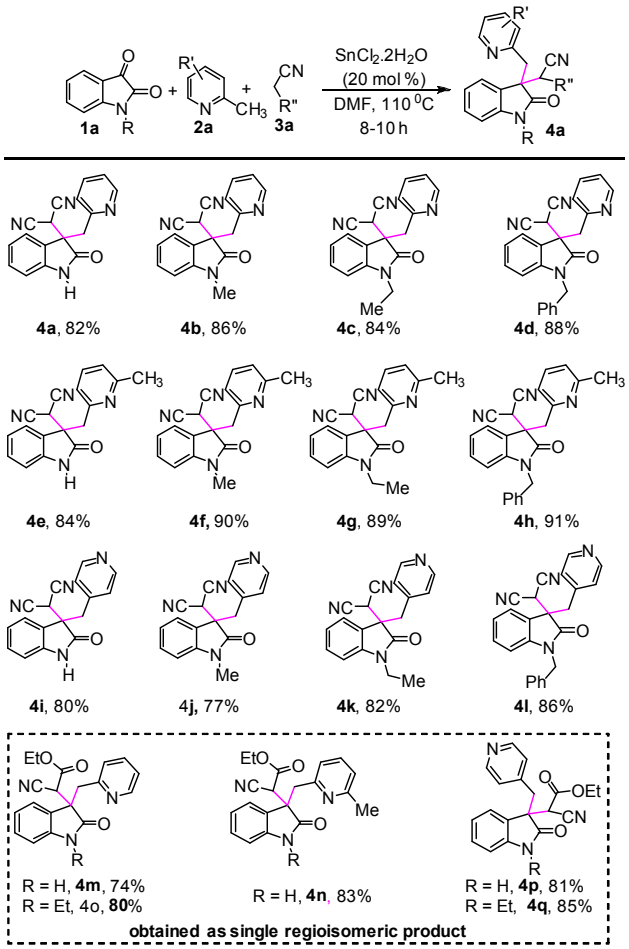
Entry	Catalyst	Solvent	Temp. (^{o}C)	Time (h)	Yield (%)[b]
1	$SnCl_2.2H_2O$	1,4 Dioxane	110	14	74
2	$SnCl_2.2H_2O$	Neat	120	20	34
3	$SnCl_2.2H_2O$	Toluene	110	14	62
4	$SnCl_2.2H_2O$	DCE	90	14	nr
5	$SnCl_2.2H_2O$	DMSO	110	14	nr
6	$SnCl_2.2H_2O$	NMP	110	14	nr
7	$SnCl_2.2H_2O$	DMF	110	10	82
8	$SnCl_2.2H_2O$	CH_3CN	85	14	nr
9	$SnCl_2.2H_2O$	THF	70	14	nr
10	$BF_3{\cdot}Et_2O$	DMF	110	14	77
11	$SnCl_4$	DMF	110	14	62
12	Cu_2O	DMF	110	14	nr
13	CuBr	DMF	110	14	nr
14	$CuBr_2$	DMF	110	14	nr
15	$CuCl_2$	DMF	110	14	nr
16	$SnCl_2.2H_2O$	DMF	90	10	32
17	$SnCl_2.2H_2O$	DMF	70	10	trace
18c	$SnCl_2.2H_2O$	DMF	110	10	47
19d	$SnCl_2.2H_2O$	DMF	110	10	26

[a]Reaction conditions: Isatin (1 mmol), 2- Picoline (1.2 mmol), Malononitrile (1.2 mmol), Catalyst (20 mol %), in Solvent (5 ml), [b]Isolated yield, [c]Catalyst (15 mol %), [d]Catalyst (10 mol %), nr = No reaction.

With the optimized reaction condition in hand, we investigated the scope of one pot tandem protocol by performing the reaction between unprotected/protected isatin **1a**, various azaarenes **2a,** and active methylene compounds **3a** (Table 2). The isatin, protected isatins (N-methyl, -ethyl, -propyl, -benzyl), and malononitrile were reacted smoothly with 2-picoline gave 82-88% yield (**4a-4d**). The electron-rich 2, 6 lutidine well tolerated for this transformation provided the desired product in excellent yield (**4e-4h**), whereas neutral 4-picoline afforded desired product in 77 to 86% yield (**4i-4l**). To our delight, 2-picoline, 4-picoline, 2, 6 lutidine, and ethylcyanoacetate were also reacting without any problem with isatin/protected isatin (N-ethyl) and provided good yield (**4m- 4q**). The

single crystal **X**-ray analysis confirmed the structure of **4q** compound (Figure 2). Inspired by these interesting results, we focused our attention to expand the scope of one pot tandem protocol to the 2(azaaryl)methanes (Table 3). Surprisingly, 2-methylbenziimidazole, malononitrile reacted successfully with isatin provided anticipated 5a functionalized spirooxindoles *via* Knoevenagel- Michael-Cyclization sequential tandem reaction.

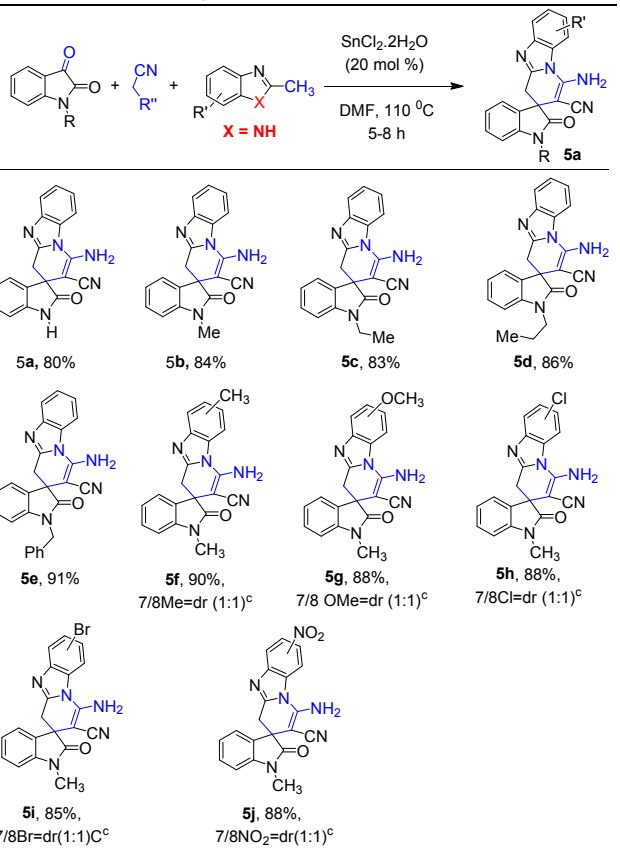
Table 2 Substrate Scope of One-Pot Tandem Process.[a,b]



[a]Reaction conditions: Isatin (1 mmol), 2(azaaryl)methanes (1.2 mmol), Malononitrile (1.2 mmol), $SnCl_2.2H_2O$ (20 mol%), DMF (5 mL), 110 ^{0}C for 8-10 h. [b] Isolated yield.

Encouraged by this result, we fascinated to further elaborate the scope tandem process for synthesis of the rich structural diverse spirooxindoles scaffold by substituting various 2-(azaaryl) methanes at the C-3 positions of isatins (Table 3). Amazingly, varoius isatin such as NH, N-methyl, N-ethyl, N-propyl, and N-benzyl reacted smoothly with 2-methyl benziimidazole afforded the desired functionalized spirooxindoles in good yields (entries **5a-5e**). The electron-rich and electron -poor derivatives of 2-methyl benziimidazole bearing various functional groups at different position of the ring are participated well in the reaction and preferentially underwent one pot tandem process with N- methyl isatin and gave the corresponding spirooxindoles as a mixture of diastereomers (d.r. =1:1) in good (85-90%) yield (entries **5f-5j**). The single crystal X-ray analysis confirmed the scaffold structure of **5d** compound (Figure 2).

Table 3 Substrate Scope of One-Pot Tandem Process.[a]



[a]Reaction conditions: Isatin (1 mmol), 2(azaaryl)methanes (1 mmol), Malononitrile (1.2 mmol), $SnCl_2.2H_2O$ (20 mol%), DMF (5 mL), 110 ^{0}C for 5-8 h. [b]Isolated yield. [c]The distereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture.

Due to the promising results, we also investigated the scope of one pot tandem protocol to 2-methyl benzothiazole, 2-methyl benzooxazole (Table **4**). Miraculously, various isatins such as (NH, N-methyl, -ethyl, -propyl, -benzyl) and malononitrile reacted well with 2-methyl benzothiazole /2-methyl benzooxazole and gave unprecedented 3, 3-disubstituted 2-oxindoles in good to excellent yields (entries **6a-6i**). Moreover, 2-methyl benzooxazole, ethylcyanoacetate reacted with N-methyl, and N-ethyl isatin gives corresponding single

regioisomeric product in 76%, and 80% yield, respectively (entry 6j, 6k).

The results in the Table 2, 3, and 4 envisaged that one-pot multi-component protocol comprising a domino Knoevenagel-Michael-Cyclization sequential tandem reaction via Sn-Catalyzed C(sp3)-H functionalization of 2-methyl azaarenes and 2-(azaaryl)methanes is unique, novel, general, efficient and well tolerated to electron-rich/electron-poor functional groups on the various substrates and allows the formation of 3, 3'-disubstituted 2-oxindole and functionalized

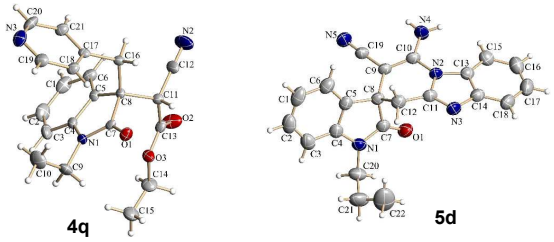
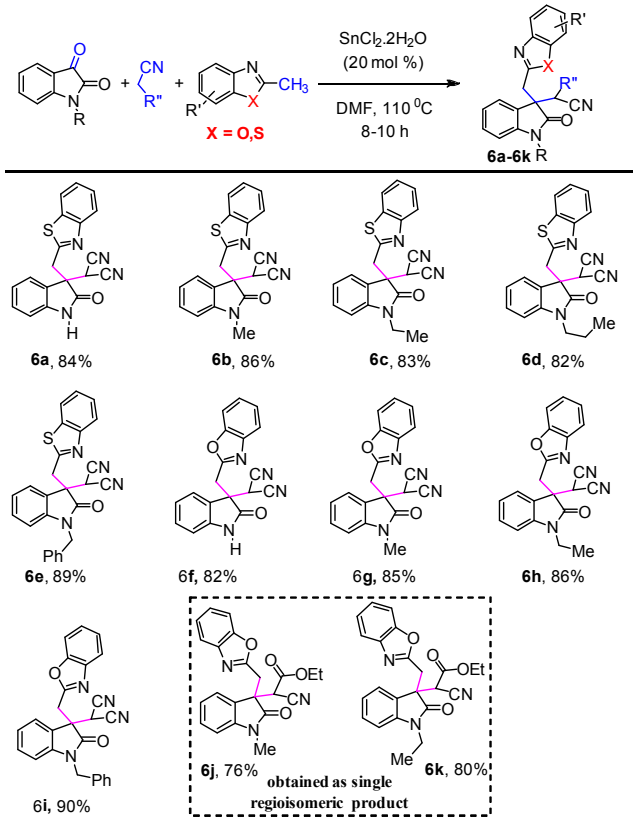


Figure 2 ORTEP Diagrams of Compound 4q and 5d

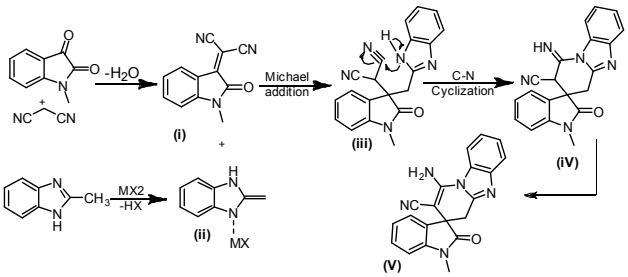
spirooxindoles scaffolds in good yields, which will be highly attractive for the design and drug discovery program.

Table 4 Substrate Scope of One-Pot Tandem Process.[a, b]



[a]Reaction conditions: Isatin (1 mmol), 2(azaaryl)methanes (1 mmol), Malononitrile (1.2 mmol), $SnCl_2.2H_2O$ (20 mol%), DMF (5 mL), 110 ^{0}C for 8-10 h. [b] Isolated yield.

As per earlier reported literature,[11] the plausible reaction mechanism outline in **scheme 2**. The predicted mechanism involves the condensation reactions of isatin with malononitrile leads to Knoevenagel adduct (i). The activation of 2-(azaaryl)methane by coordination of catalyst to generate metal enamide (**ii**).[12] The metal enamide (**ii**) undergoes addition reaction with adduct (i) to generate 3, 3'-disubstituted 2-oxindole (**iii**),



Scheme 2 Proposed Mechanism for C-H Functionaliza-tion of 2(azaaryl)methanes

which then proceed via Michael addition-intramolecular C-N cy-clization provide an intermediate (**iv**) followed by 1, 3 hydrogen shift to give final spirooxindoles scaffold (**v**).

In conclusion, a novel, efficient, general one pot MCR protocol comprising a domino Knoevenagel-Michael-cyclization sequential tandem reaction of various isatin, active metnylene compounds with various 2-methyl azaarenes and 2-(azaaryl)methanes via Sn-Catalyzed C(sp3)-H functionalization has been developed for the synthesis of biologically relevant 3, 3'-disubstituted-2-oxindoles /spirooxindoles scaffold in good to excellent yield. The developed MCR strategy is practical, cost-effective and atom economical and provides new access to important 3,3'-disubstituted 2-oxindoles/spirooxindoles scaffolds.

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