$TiCl_4$ catalyzed tandem construction of C–C and C–O bonds: a simple and one-pot atom-economical stereoselective synthesis of spiro-oxindoles†

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An atom-economical stereoselective synthesis of [{1-acetyl-5-methyl-6,8-dioxabicyclo(3.2.1) octane}-7-spiro-3′-(indolin-2′-one)] derivatives, containing both the oxindole and 6,8-dioxabicyclo(3.2.1)octane moieties *via* $TiCl_4$ catalyzed coupling of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran with isatin derivatives is described.

Spiro-oxindole[1] framework occupies a special place in heterocyclic chemistry because of the presence of this framework in a number of natural products such as surugatoxin, horsfiline, spirotryprostatin A&B, elacomine, gelsamine, alstonisine, strychnofoline and tasmanin. The 6,8-dioxabicyclo[3.2.1]octane moiety[2] represents yet another important structural organization (assembly) present in a number of pheromones and natural products such as *exo*-brevicomin, frontalin, multistriatin, bullerone and palytoxin. Due to the importance of these two structural frameworks *i.e.*, spiro-oxindole and 6,8-dioxabicyclo[3.2.1]octane moieties, development of simple and convenient methodologies for synthesis of these structural assemblies continues to be a challenging area in organic chemistry.[1f,g,3,4] It occurred to us that development of simple synthesis for aesthetically appealing molecular architecture containing both the oxindole moiety and 6,8-dioxabicyclo[3.2.1]octane framework linked with an interesting and appropriate spiro-bridge represents an attractive endeavor in organic and medicinal chemistry. In continuation of our interest in developing one-pot methodologies for synthesis of heterocyclic molecules,[5] we herein report a novel, simple, convenient and one-pot methodology for synthesis of molecules containing both the oxindole and 6,8-dioxabicyclo[3.2.1]octane moieties with an aesthetically appealing spiro-bridge *via* the titanium tetrachloride catalyzed aldol reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran with various isatin derivatives, involving tandem construction of C–C and C–O bonds.

After considering some possible retro-synthetic strategies for synthesis of [6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(indolin-2′-ones), we arrived at the retro-synthetic strategy shown in Scheme 1 which will probably involve aldol reaction of 2-alkanoyl-6-alkyl-2,3-dihydro-4*H*-pyrans with isatin derivatives, followed by cyclization to provide the desired spiro-oxindole derivatives.

† Electronic supplementary information (ESI) available: representative experimental procedure, spectral data for all compounds **3–11** and **13**. Crystallographic information data files (CIF's) for compounds **3**, **11** and **13** with ORTEP diagrams. See http://www.rsc.org/suppdata/cc/b5/b500224a/

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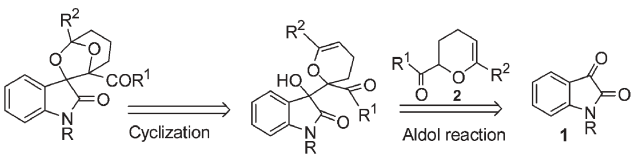
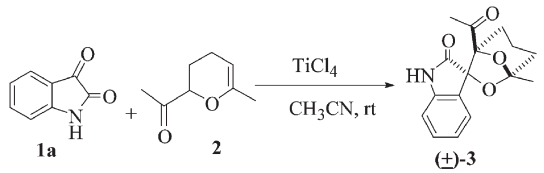
Our earlier work[5d] on the $TiCl_4$ mediated Baylis–Hillman reaction[6] and our recent work[6g] on the steric factors directed Baylis–Hillman or aldol reactions between cyclohex-2-enones and α-keto esters under the influence of $TiCl_4$, led us to examine the possible aldol reaction[7] between 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**, $R^1 = R^2 = Me$) (Diels–Alder dimer of methyl vinyl ketone) and isatin derivatives under the influence of titanium tetrachloride, as this strategy might provide one-pot synthesis of the desired spiro-oxindole derivatives[8] [1-acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(indolin-2′-ones) with stereocontrol during the formation of C–C and C–O bonds. In this direction we have first carried out the reaction of isatin (**1a**) with various quantities of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) under the influence of different quantities of $TiCl_4$ (Table 1). The best results were obtained when isatin (**1a**) (1 mmol) was treated with 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) (2 mmol) in acetonitrile as solvent in the presence of $TiCl_4$ (20 mol%, 0.2 mmol, 2 M solution in CH_2Cl_2) at room temperature for 6 h, thus providing the desired product, [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*][9]-[1-acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(indolin-2′-one) (**3**) in 74% yield after usual work-up and purification through silica gel column chromatography (entry 5, Table 1, Scheme 2). The structure and stereochemistry of this molecule were further confirmed by single crystal X-ray data[10,11] (see ESI† & Fig. 1)



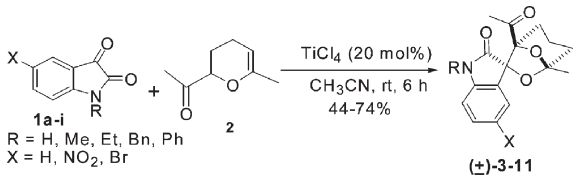
Scheme 1 Schematic representation of retro-synthetic strategy for spiro-oxindoles.

Table 1 The influence of various quantities of $TiCl_4$ in the reaction of isatin (**1a**) with different quantities of **2** in CH_3CN at room temperature for 6 h (Scheme 2)

Entry	Isatin **1a** (mmol)	**2** (mmol)	$TiCl_4$ (mmol)	Isolated yield of **3** (%)
1	1	2	1	24
2	1	2	2	32
3	1	5	1	73
4	1	1	0.2	49
5	**1**	**2**	**0.2**	**74**
6	1	1.2	0.1	43



Scheme 2



Scheme 3 Stereoselective synthesis of functionalized (±)-spiro-oxindoles.

We have then successfully extended this methodology to various isatin derivatives **1b–i** to provide representative spiro-oxindole derivatives **4–11** in 44–70% yields (Scheme 3, Table 2).[12] We have also confirmed the structure and stereochemistry in the case of molecule **11** by single crystal X-ray data[10,11] (see ESI† & Fig. 1).

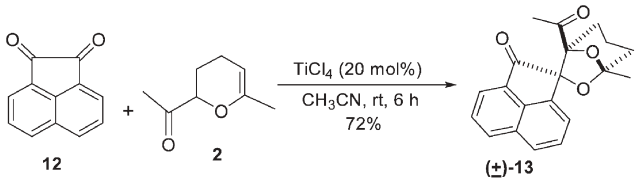
With a view to understanding the generality of this methodology, we have also extended this strategy to acenaphthenequinone (**12**). Thus, reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) with dione **12** under the catalytic influence of $TiCl_4$ (20 mol%) provided the desired spiro derivative, [1*S*,5*S*,7(1′)*S*/1*R*,5*R*,7(1′)*R*]-[1-acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-1′-(1′,2′-dihydroacenaphthalene-2′-one) (**13**) in 72% isolated yield (Scheme 4, Table 2). The structure and stereochemistry of this molecule were further confirmed by single crystal X-ray data[10,11] (see ESI† & Fig. 1).

A plausible mechanism for the formation of spiro-oxindole derivatives is presented in Scheme 5. The reaction might possibly be proceeding through transition state **A** leading to the desired spiro-oxindole products with *S,S,S*/*R,R,R* stereo-chemistry *via* the more favored transient intermediate **B**. With a view to understand the nature of the actual species formed in the reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) with $TiCl_4$, we have recorded the ^{1}H NMR and ^{13}C NMR spectra of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) (1.0 eq.) in the presence of $TiCl_4$ (0.1 eq.) (the ratio of **2** and $TiCl_4$ is 1:0.1) in $CDCl_3$. The spectral data clearly indicate the possible formation of titanium enolate or complexation of $TiCl_4$ with **2** (see ESI†). We have also recorded the ^{1}H NMR and ^{13}C NMR spectra of 1-methylisatin (**1b**) (1.0 eq.) in the presence of $TiCl_4$ (0.2 eq.) in $CDCl_3$. The data show that there is no significant change in the chemical shift values and also in the pattern of the peaks from the original spectrum, thus indicating the absence of any strong complexation between **1b** and $TiCl_4$. However, we cannot rule out some kind of complexation between **1b** and $TiCl_4$ (see ESI†).

Table 2 Stereoselective synthesis of functionalized (±)-spiro-oxindoles[12] *via* the reaction of **2** with **1a–i** or **12**[a]

Isatin/Dione	X	R	Product[b]	Isolated yield (%)	mp/°C
1a	H	H	**3**[c]	74	163–165
1b	H	Me	**4**	64	148–150
1c	H	Et	**5**	69	131–132
1d	H	Bn	**6**	70	141–143
1e	H	Ph	**7**	56	125–126
1f	NO_2	H	**8**	48	214–216
1g	NO_2	Et	**9**	50	168–170
1h	Br	Me	**10**	61	179–180
1i	Br	Et	**11**[c]	44	137–140
12	—	—	**13**[c]	72	147–149

[a] All reactions were carried out on 1 mmol scale of isatin derivatives (**1a–i**) and **12**, with 2 mmol of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) in the presence of 20 mol% $TiCl_4$ at room temperature for 6 h. [b] All the compounds were fully characterized (see ESI). [c] Structures of these molecules were further established by the single crystal X-ray data.[10,11]



Scheme 4

In conclusion, we have developed a simple, convenient, and one-pot atom economical stereoselective synthesis of spiro-oxindoles *via* the titanium tetrachloride catalyzed coupling (aldol reaction) of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran with various isatin derivatives, involving tandem construction of C–C and C–O bonds.

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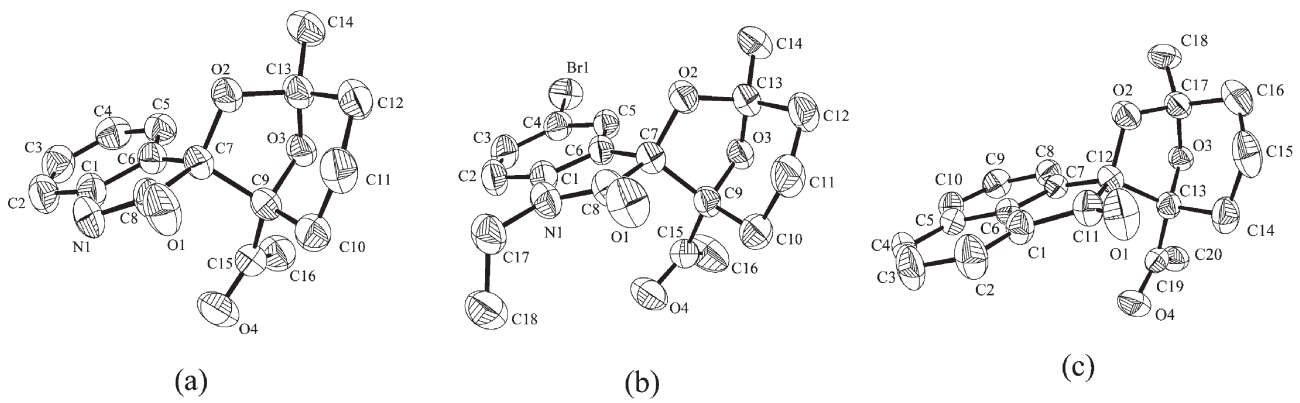
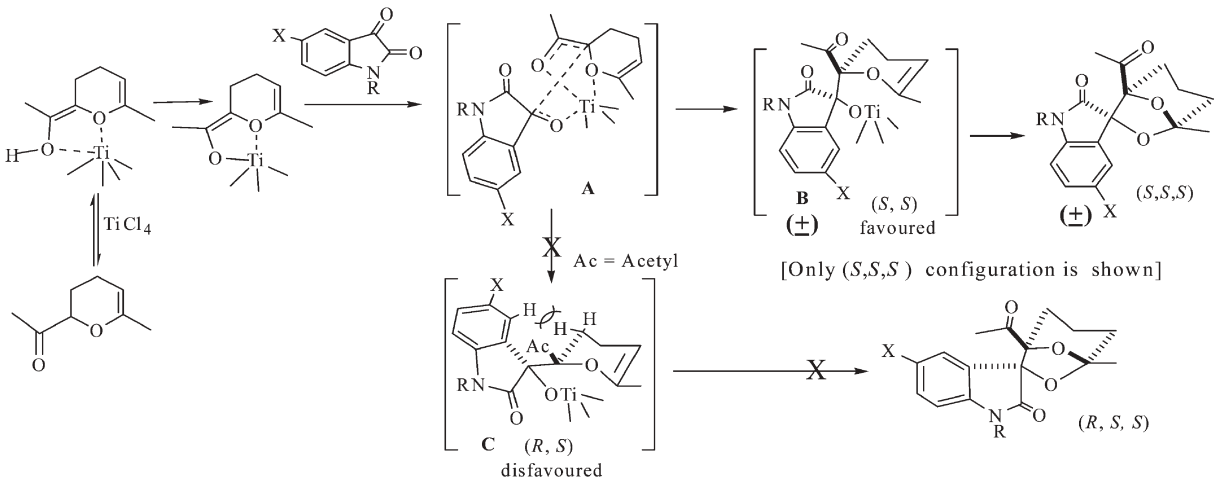


Fig. 1 ORTEP diagrams of (a) **3**, (b) **11** and (c) **13**.



Scheme 5 Plausible mechanism for the formation of (±)-spiro-oxindoles.

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8 Recently Nair & co-workers reported spiro-oxindole synthesis containing 6,8-dioxabicyclo[3.2.1]octane moiety *via* facile dipolar cycloaddition reactions of isatins with carbonyl ylides, generated by $Rh_2(OAc)_4$ catalyzed reaction of α-diazo ketones. [Ref: V. Nair, K. C. Sheela, D. Sethumadhavan, S. Bindu, N. P. Rath and G. K. Eigendorf, *Synlett.*, 2001, 272].

9 We have written [1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*] before all the names of spiro-oxindoles to indicate the racemic nature and also stereochemistry.

10 Intramolecular bond parameters for all the structures (**3**, **11** & **13**) determined by X-ray crystallography are unexceptional.

11 Detailed X-ray crystallographic data are available for compounds **3** (CCDC 248071), **11** (CCDC 248072), and **13** (CCDC 248073). See ESI.

12 The stereochemistry of the products **4**–**10** was assigned in analogy with **3** and **11**.