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ARTICLE TYPE

$In(OTf)_3$-Catalyzed synthesis of 2-styryl quinolines: Scope and limitations of metal Lewis acids for tandem Friedländer annulation-Knoevenagel condensation

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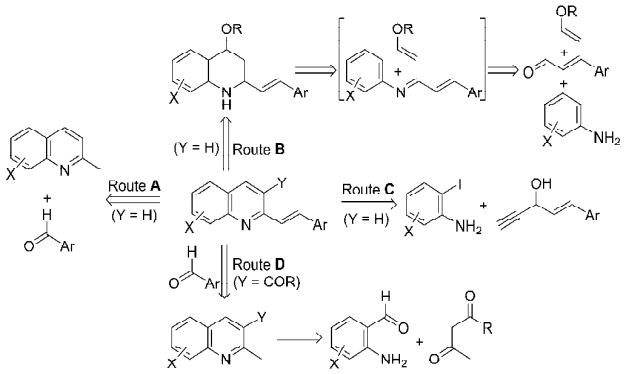
The catalytic potential of different metal Lewis acids has been assessed for the one-pot tandem Friedländer annulation and Knoevenagel condensation involving 2-aminobenzophenone, ethyl acetoacetate, and benzaldehyde to form 2-styryl quinoline under solvent free condition. While various metal Lewis acids were effective in promoting the Friedländer annulation step, $In(OTf)_3$ was the only effective catalyst for the subsequent Knoevenagel condensation reaction suggesting $In(OTf)_3$ as the stand-alone catalyst for the tandem Friedländer-Knoevenagel reaction to form 2-styryl quinolines. The protocol is compatible with different variation of aromatic/hetero-aromatic aldehydes and α, β unsaturated aromatic aldehyde giving highly functionalized 2-aryl/heteroaryl vinyl quinolines. The catalyst can be recovered and reused to afford the desired product in very good to excellent yields.

Introduction

Quinolines are important class of *N*-heterocyclic compounds because of the wide occurrence of the quinoline moiety in natural products[1] and biologically active compounds.[2] Amongst the various quinoline derivatives, the 2-styryl quinolines (SQLs) continue to draw interest to synthetic organic/medicinal chemists as they have emerged as a new class of HIV-integrase inhibitors devoid of cytotoxicity.[3] The reported synthesis of SQLs (Scheme 1) are the (i) classical Knoevenagel condensation of 2-methylquinolines with an aldehyde in acetic anhydride under reflux (140 °C) for a prolonged period (~ 16 h) (Route A)[3] (ii) two stage process of ceric ammonium nitrate (CAN)-catalyzed vinylogous type-II Povarov reaction involving arylamines, cinnamaldehydes, and vinyl ethers to form the intermediate tetrahydroquinolines followed by DDQ-promoted dehydrogenative aromatization (Route B),[4] and (iii) microwave-assisted coupling-isomerization reaction (MACIR) involving 2-bromo/iodo aniline and substituted propargyl alcohols in the presence of transition metal catalysts and DBU (2 equiv) (Route C).[5]



Scheme 1. Various strategies for the synthesis of 2-styryl quinoline

These reported procedures have several drawbacks: (i) the lack of commercial availability of the starting materials such as the 2-methylquinolines (Route A) and the 2-styryl propargyl alcohols (Route C) which would require additional synthetic efforts; (ii) the use of costly transition metal catalysts and large excess of organic base (DBU) (Route C); (iii) requirement of stoichiometric quantities of toxic DDQ as dehydrogenating agent to convert the intermediately formed tetrahydroquinoline to quinoline (Route B); (iv) necessity of special apparatus (e.g., microwave reactor) (Route C); (v) high reaction temperature, prolonged reaction period, and the use of volatile organic solvents (THF, DCM) etc. The reaction sequence under route B may also proceed via the alternative diene framework (the exocyclic α,β-unsaturated imine system) involving inverse electron demand Diels–Alder (DA_{INV}) reaction leading to form 1,4-dihydropyridines (**I**) as the side products (Scheme 2).[6] Further, the Route B may also lead to the formation of 2-methyl-1,2,3,4-tetrahydroquinolines (**II**) as side

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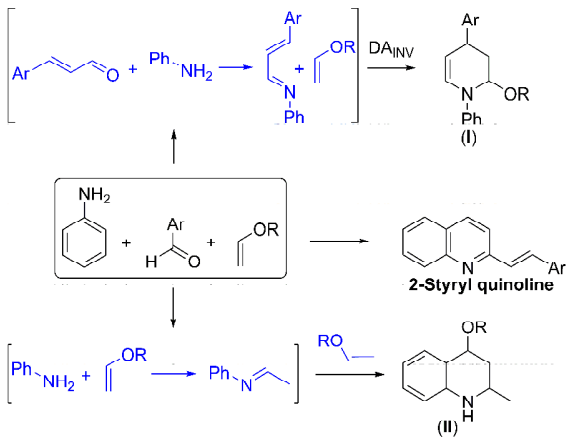
product via the cycloaddition reaction between the vinyl ether and the in situ formed imine (due to the CAN-catalysed reaction between the aryl amine and another molecule of the vinyl ether) that decreases the overall yield of the desired SQLs (Scheme 2).[7]



Scheme 2. Formation of side products during the CAN-catalysed vinologous type-II Povarov reaction following Route B under Scheme 1.

A direct synthesis following Route D involving the one-pot tandem Friedländer annulation-Knoevenagel condensation sequence would provide a convenient synthesis of the 2-SQLs and offer means for diversification to generate functional materials and broaden the scope for pharmacophoric modification (Figure 1).

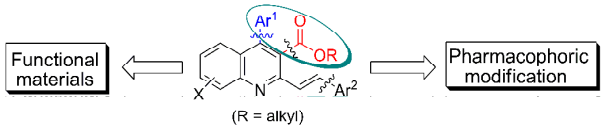


Figure 1. Scope for structural diversification of 2-styryl quinolines obtained by Route D under Scheme **1**.

In order to overcome the drawbacks of the reported procedures the Route D appears to be suitable but there is only one report.[8] Thus, a convenient, rapid and high yielding synthetic method is needed to fulfill the timely supply of the designed molecules for biological evaluation[9] and enrichment of medicinal chemists' tool box.[10] Herein we describe an extremely efficient catalytic procedure for the domino synthesis of 2-SQLs with structural diversity.

Results and Discussion

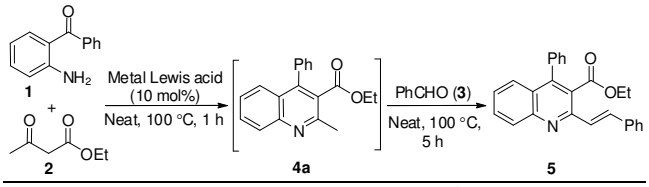
In search for a more convenient and improved method of synthesis for the titled compounds following the one-pot tandem reaction strategy (Route D, Scheme 1) it was considered that suitable catalytic assistance during the Friedländer annulation and Knoevenagel condensation steps would offer high yields in shorter period under milder reaction conditions.

The adverse effect of the manufacturing processes of drugs and pharmaceuticals on the environment urges for sustainable development.[11] The major drive towards this initiative is the replacement of volatile organic solvents (VOSs) by solvent free condition[12] as VOSs are major contributors to environmental pollution due to their abundant use (more than 85% of the total mass utilization of a chemical process) and incomplete recovery efficiency (50 - 80%).[13]

It was hypothesized that a catalyst which acts via the electrophilic activation strategy would promote both the steps, the Friedländer annulation (step 1) and the Knoevenagel condensation reaction (step 2). In a model study the tandem Friedländer annulation-Knoevenagel condensation reaction involving 2-aminobenzophenone **1**, ethyl acetoacetate **2**, and benzaldehyde **3** used in equimolar amounts was performed at 100 °C under solvent free condition in the presence of various metal halides, tetrafluoroborates, perchlorates, and triflates (Table 1). Since the reaction is expected to proceed via the intermediate formation of the 2-methylquinoline derivative **4a** to afford the final 2-SQL **5**, in each case the progress of the reaction was monitored by GC-MS to assess the conversion to **4a** after 1 h of the treatment of **1** with **2** followed by addition of **3** and isolating **5** after another 5 h.

Most of the metal salts exhibited good catalytic potential to promote the Friedländer annulation (70-100% GC-MS conversion to **4a**). However, $In(OTf)_3$ emerged as the stand-alone catalyst for the tandem Friedländer annulation-Knoevenagel condensation to afforded **5** in excellent yield (82%). The next best results (63-70% yields) were obtained with $InCl_3$, $Mg(OTf)_2$, $Sc(OTf)_3$, $In(ClO_4)_3$, and $Mg(ClO_4)_2·6H_2O$, respectively. The results further reveal that the Knoevenagel condensation step is the most critical stage of the tandem process for the one-pot synthesis of 2-styryl quinolines

Table 1. Assessment of the catalytic potential of different metal Lewis acids and [Hmim]TFA for one-pot tandem Friedländer annulation-Knoevenagel condensation involving **1**, **2**, and **3** to form the 2-styryl quinoline **5** via the 2-methylquinoline **4a**.[a]



Entry	Catalyst	**4a**/Yield (%)[b]	**5**/Yield (%)[c]
1	$Fe(BF_4)_2·xH_2O$	70	25
2	$Zn(BF_4)_2$	100	30
3	$AgBF_4$	83	35
4	$Cu(BF_4)_2$	85	36
5	$Co(BF_4)_2$	75	31
6	$LiClO_4$	40	traces
7	$Fe(ClO_4)_3·xH_2O$	75	25
8	$Zn(ClO_4)_2·xH_2O$	100	35
9	$ZrO(ClO_4)_3·xH_2O$	82	traces
10	$Bi(ClO_4)_3·xH_2O$	80	25
11	$Mg(ClO_4)_2·6H_2O$	96	60
12	$Cu(ClO_4)_2·6H_2O$	88	42
13	$In(ClO_4)_3·6H_2O$	85	61
14	$Zn(OTf)_2$	100	45
15	$Mg(OTf)_2$	94	68
16	$Yb(OTf)_3·xH_2O$	86	35
17	$Eu(OTf)_3$	89	36
18	$Er(OTf)_3$	96	25
19	AgOTf	73	20
20	$In(OTf)_3$	100	82
21	$Cu(OTf)_2$	92	30
22	$Sc(OTf)_3$	94	65
23	$Gd(OTf)_3$	99	35
24	$La(OTf)_3$	88	20
25	$Sm(OTf)_3$	94	45
26	$Er(OTf)_3$	96	52

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27	$Dy(OTf)_3$	99	36
28	$Nd(OTf)_3$	92	41
29	$Ho(OTf)_3$	87	52
30	$Al(OTf)_3$	98	50
31	$ZrCl_4$	84	20
32	$GaCl_3$	84	35
33	$NbCl_5$	72	32
34	$HfCl_4$	99	44
35	InF_3	92	62
36	$InCl_3$	96	68[d]
37	$InBr_3$	84	58
38	InI_3	85	55
39	$In(NO_3)_3 \cdot xH_2O$	78	55
40	$In(OAc)_3$	72	48
41	In (powder)	52	traces
42	In (pieces)	35	traces
43	None	3	traces
44	[Hmim]TFA	nil	nil[e]
45	[Hmim]TFA	90	80[f]
46	CF_3CO_2H	nil	nil[g]

[a] **1** (0.197 g, 1 mmol) was treated with **2** (0.13 g, 1 mmol, 1 equiv) in the presence of different metal Lewis acid (10 mol%) under neat condition at 100 °C (oil bath) for 1 h followed by addition of **3** (0.106 g, 1 mmol, 1 equiv) and continuation of the reaction for further 5 h. [b] Conversion to **4a** (GC-MS). [c]Isolated yield of **5**. [d]The yields of **5** were 41 and 72% in performing the reaction for 2 and 10 h, respectively. [e]The reaction was carried out using 10 mol% of [Hmim]TFA. [f]The reaction was carried out using 50 mol% of [Hmim]TFA. [g]The reaction was carried out using 50 mol% of TFA.

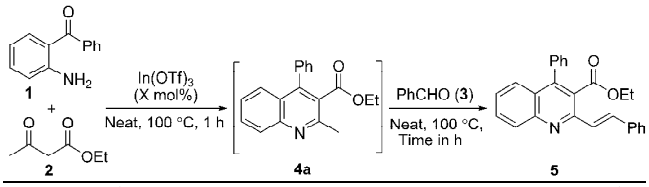
We observed that the only report on the synthesis of 2-styryl quinolines following this strategy involves the use of 50 mol% of the ionic liquid (IL) [Hmim]TFA.[8] Thus, a comparison of the catalytic efficiency of [Hmim]TFA with that of $In(OTf)_3$ is relevant. The use of 10 mol% of [Hmim]TFA did not produce any significant amount of **5** (table 1, entry 44) suggesting its inefficiency for catalytic purpose that establishes the superiority of $In(OTf)_3$. To assess whether the ability of [Hmim]TFA, used in 50 mol%, to form **5** could be due to the associated trifluoroacetic acid (used in molar equivalent with imidazole to form [Hmim]TFA) the reaction was performed in the presence of 50 mol% of trifluoroacetic acid. However, no significant amount of **5** was obtained (table 1, entry 46). This indicated that the comparable yield (table 1, entry 45) obtained in using [Hmim]TFA (50 mol%) may not be a general Brönsted acid-catalysed event and could be due to the hydrogen bond (HB) formation ability of the Hmim cation through its C-2 proton.[14]

We have demonstrated that the HB formation ability of the C-2 proton of the MeIm cation plays significant role in attributing the organo-catalytic potential of *N*-methylimidazole-based ILs in promoting various organic reactions.[15] The influence of HB also plays critical/significant role in various organic reactions under metal-free[16] or metal-assisted[17] environment. However, in the present case the requirement of 50 mol% of [Hmim]TFA as the hydrogen-bond mediated electrophilic activation agent reveals the requirement of a more stronger electrophilic activation catalyst. This brings the rationale of selecting metal-derived Lewis acid catalysts and $In(OTf)_3$ is found to be the most effective catalyst.

The Friedländer annulation to form 2-methylquinolines has been reported in the presence of $Zn(OTf)_2$ under microwave irradiation.[18] Although the conversion to **4a** (table 1, entry 14) is in agreement with the catalytic potential of $Zn(OTf)_2$ for 2-methylquinolines formation via the Friedländer annulations, the poor yield (45%) of **5** demonstrates the distinctiveness of $In(OTf)_3$ as the most effective catalyst for the tandem Friedlander annulation-Knoevenagel condensation process.

To derive the best operative reaction condition for the $In(OTf)_3$-catalysed synthesis of the 2-SQLs following the route D (Scheme 1) the two-stage systematic Friedländer annulations-Knoevenagel condensation reaction of **1**, **2**, and **3** to form **5** was performed under different variation of the various reaction parameters such as the reaction temperature, the amount of $In(OTf)_3$, and the reaction medium (table 2). The optimum reaction temperature was found to be 100 °C as the increase of the reaction temperature to 120-150 °C (entries 6 and 7, table 2) did not show any significant increase in the yield which, however, decreased significantly on lowering the reaction temperature to 50-80 °C (entries 2 and 3, table 2). No product formation was observed in carrying out the reactions at rt (entry 1, table 2). The optimum catalyst amount was found to be 10 mol%. The use of lesser amount (2.5-7.5 mol%) of $In(OTf)_3$ afforded **5** in decreased yields (entries 8-13, table 2) and no promising results obtained on prolonging the reaction for further 10 h. No improvement in the product yield was observed using larger amount (15 mol%) of $In(OTf)_3$ (entry 14, table 2). The use of solvents (hydrocarbon, halogenated hydrocarbon, ethereal, protic polar and aprotic polar) in general showed detrimental effect (entry 15-23, table 2).

Table 2. Optimisation of the various reaction parameters during the $In(OTf)_3$-catalysed one-pot tandem Friedländer annulation-Knoevenagel condensation involving **1**, **2**, and **3** to form **5**.[a]



Entry	X[b]	Solvent	Temp (°C)[c]	Time (h)	Yield(%)[d]
1	10	neat	rt (25 -30)	5	traces
2	10	neat	50	5	20
3	10	neat	80	5	61
4	10	neat	100	5	82
5	10	neat	100	2	80
6	10	neat	120	5	82
7	10	neat	150	5	82
8	2.5	neat	100	5	32
9	2.5	neat	100	10	41
10	5	neat	100	5	45
11	5	neat	100	10	56
12	7.5	neat	100	5	62
13	7.5	neat	100	10	71
14	15	neat	100	5	82
15	10	PhMe	100	5	20
16	10	DCM	reflux	5	35
17	10	Dioxane	reflux	5	37
18	10	THF	reflux	5	traces
19	10	EtOH	reflux	5	traces
20	10	Water	reflux	5	traces
21	10	MeCN	reflux	5	26
22	10	DMSO	100	5	traces
23	10	DMF	100	5	15

[a] **1** (0.197 g, 1 mmol) was treated with **2** (0.13 g, 1 mmol, 1 equiv) in the presence of $In(OTf)_3$ under different operating conditions for 1 h followed by addition of **3** (0.106 g, 1 mmol, 1 equiv) and continuation of the reaction for further 5 h. [b] Mol% of the catalyst. [c]Oil bath temp. [d]Isolated yield of **5**.

The optimum time period required for the individual step of

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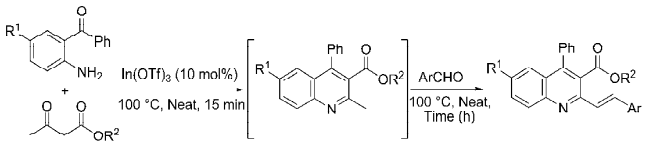
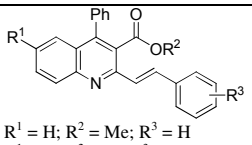
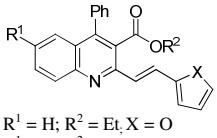
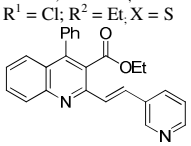
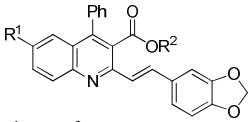
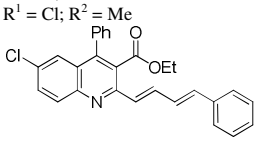
tandem process (step 1: Friedländer annulation and step 2: Knoevenagel condensation) was determined by monitoring (GC-MS) the progress of the $In(OTf)_3$-catalysed synthesis of **5** from the reaction of **1**, **2**, and **3**. However, as **5** does not elute under GC-MS condition the progress towards the formation of **4a** was determined by GC-MS. Aliquot portions of the reaction mixture during the initial treatment of **1** with **2** at 100 °C under neat condition were withdrawn after 5, 10, and 15 min and was subjected to GC-MS analyses that indicated 43, 73, and 100% conversion to **4a**. Thus, the optimal time for the Friedländer annulation step to form the intermediate quinoline was determined as 15 min. Thereafter, separate reactions were carried out to estimate the optimal time for the formation of the 2-styryl quinoline by the reaction of the intermediately formed quinoline **4a** with the aldehyde **3**. On each occasion, **3** was added after 15 min of the treatment of **1** with **2** at 100 °C under neat condition in the presence of $In(OTf)_3$ (10 mol%) and the reaction was continued for further time period as indicated and the yield was estimated after isolating **5**. The optimum time for Knoevenagel condensation was found to be 2 h (81% yield) as the yield of **5** decreased in reducing the reaction time (28, 43, 66, and 72% after 60, 75, 90, and 105 min, respectively) and no enhancement of yield was observed in prolonging the Knoevenagel condensation reaction (81 and 82% after 135 and 150 min, respectively).

Next the applicability of the $In(OTf)_3$-catalysed tandem Friedländer annulation-Knoevenagel condensation was extended for the generalised one-pot synthesis of differently substituted 2-SQLs (Table 3). The reactions proceeded well with substituted aldehydes bearing electron donating group (entries 4, 5, 15, and 16, table 3), electron withdrawing group (entries 6 and 7, table 3), halogens (entry 8-10, table 3), and as well as with different heterocyclic aldehydes such as furan-2-carboxaldehyde (entry 11; table 3), thiophene-2-carboxaldehyde (entries 12 and 13, table 3), and pyridine-4-carboxaldehyde (entry 14, table 3) to afford the desired 2-SQLs in excellent yields. The reactions were also compatible with aldehyde containing acid sensitive dioxalone group (entries 15 and 16, table 3) and as well as with α, β-unsaturated aromatic aldehyde (entry 17, table 3). However, with aliphatic aldehydes such as *iso*-butyraldehyde and cyclohexane carboxaldehyde the 2-SQL formation did not occur and the isolated product was identified as the intermediate 2-methylquinoline **4a**. A few representative reactions were carried out using chloro substituted 2-aminobenzophenone and excellent yields were obtained (entry 3, 7, 13, 16 and 17; table 3). With respect to the variation in the β-ketoester, reactions proceeded well for methyl and ethyl acetoacetates. However no 2-SQL product was formed by using ^{t}-butyl acetoacetate and *β*-diketones such as acetyl acetone and benzoyl acetone. In the case of benzoyl acetone, the corresponding intermediately formed Friedländer product was isolated. In case of acetyl acetone, a complex mixture of products was obtained which could not be purified further.

Table 3. One-pot synthesis of 2-styryl-quinolines.[a]



Entry	Product	Time (h)[b]	Yield (%)[c]
			
1	R^1 = H; R^2 = Me; R^3 = H	2	80
2	R^1 = H; R^2 = Et; R^3 = H	2	82
3	R^1 = Cl; R^2 = Et; R^3 = H	2	82
4	R^1 = H; R^2 = Et; R^3 = 4-Me	2	81
5	R^1 = H; R^2 = Et; R^3 = 4-OMe	4	75
6	R^1 = H; R^2 = Me; R^3 = 2-NO_2	2	83
7	R^1 = Cl; R^2 = Me R^3 = 4-CF_3	2	79
8	R^1 = H; R^2 = Et; R^3 = 4-F	2	82
9	R^1 = H; R^2 = Et; R^3 = 4-Cl		84
10	R^1 = H; R^2 = Et; R^3 = 4-Br	2	81
			
11	R^1 = H; R^2 = Et, X = O	4	72
12	R^1 = H; R^2 = Me, X = S	3	73
13	R^1 = Cl; R^2 = Et, X = S	3	70
			
14		4	70
			
15	R^1 = H; R^2 = Et	3	81
16	R^1 = Cl; R^2 = Me	3	81
			
17		4	76

[a]2-Aminobenzophenone (2.5 mmol) was treated with *β*-ketoester (2.5 mmol, 1 equiv) in the presence of $In(OTf)_3$ (10 mol%) at 100 °C (oil bath) for 15 min followed by addition of the aldehyde (2.5 mmol, 1 equiv) and continued stirring for the stipulated time. [b]The refer time indicate the time after addition of the aldehyde. [c]Isolated yield of the product.

To account for the failure of formation of the desired 2-SQLs in case of ^{t}-butyl acetoacetate, acetyl acetone, and benzoyl acetone the corresponding 2-methylquinolines (**4c-e**) were prepared by treatment with **1** following the Friedländer annulations. The preformed 2-methylquinolines (**4a-e**) were subjected to Knoevenagel condensation with **3** to form the 2-SQLs. The desired 2-SQLs were obtained in excellent yields from **4a** and **4b** but no significant amount of the corresponding 2-SQLs were formed from **4c-e** (Table 4). In case of **4c** and **4e** the starting material remained intact and was recovered but a complex product mixture was formed from **4d**.

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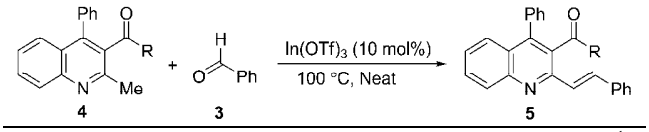
Table 4. The $In(OTf)_3$-catalysed Knoevenagel condensation of preformed **4a**-**e** with **3** to form the corresponding 2-SQLs.[a]



4 3 5

Entry	2-Methyl quinoline (**4**)	Product (**5**)	Yield (%)[b]
1	**4a:** R = OMe	**5a:** R = OMe	82
2	**4b:** R = OEt	**5b:** R = OEt	81
3	**4c:** R = OBu^{-t}	**5c:** R = OBu^{-t}	nil[c]
4	**4d:** R = Me	**5d:** R = Me	nil[d]
5	**4e:** R = Ph	**5e:** R = Ph	nil[c]

[a]2-Methyl quinoline **4** (1 mmol) was treated with **3** (1 mmol, 1 equiv) in the presence of $In(OTf)_3$ (10 mol%) at 100 °C (oil bath) for 2 h under neat condition. [b]Isolated yield of the product **5**. [c]Starting materials remained intact and was recovered. [d]Complex product mixture was obtained which could not be purified further.

Thus the lack of formation of the 2-SQLs in case of ^{t}-butyl acetoacetate and benzoyl acetone is due to the steric hindrance exhibited by the OBu^{t} and the phenyl groups of **4c** and **4e** during the Knoevenagel condensation with **3**. The complex product mixture obtained in case of acetyl acetone might be due to the competitive reaction of **3** with the 2-Me and COMe groups in **4d**.

Recycling and reuse of catalyst is an important issue in the context of green chemistry. After completion of the reaction, the reaction mixture was diluted with ethanol and the resulting supernatant liquid was filtered out. The residue was treated with ethanol twice and in each case the supernatant liquid was filtered out. The combined ethanolic extracts were evaporated to dryness and the residue was re-crystallized form ethanol-water (9:1) to obtain the desired product. The solid residue that remained in the reaction flask was collected, washed with ethanol to remove the traces of organic residues and dried to recover $In(OTf)_3$. Fresh batches of reactions involving **1**, **2** and **3** were performed using the recovered $In(OTf)_3$ to afforded **5** in good to excellent yields (Table 5).

Table 5. Investigation into the reuse of $In(OTf)_3$.[a]

Entry	Run	Yield (%)[b]
1	1st	81
2	2nd	80
3	3rd	76
4	4th	70

[a]**1** was treated with **2** (1 equiv) in the presence of $In(OTf)_3$ (10 mol%) at 100 °C (oil bath) for 15 min followed by addition of **3** (1 equiv) and the stirring was continued for the further 3 h.[b] Isolated yield of **5**.

Conclusions

The present work describes the first time investigation of metal Lewis acid catalysis for the one-pot domino syntheses of 2-styryl quinolines involving tandem Friedländer annulation and Knoevenagel condensation and found $In(OTf)_3$ to be the stand-alone catalyst for the formation of 2-SQLs. The catalyst can be recovered and reused to afford the desired product in very good to excellent yields. The new catalytic procedure offers the following distinct advantages: (i) one pot tandem synthesis of 2-styryl quinolines with broad substrate scope, (ii) no requirement of additional reagent, and (iii) solvent free condition that fulfill the triple bottom line philosophy of green chemistry.[19]

Experimental section

General remarks:

The glassware used was thoroughly washed and dried in an oven and the experiments were carried out with required precautions. Chemicals and all solvents were commercially available and used without further purification. The NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ or $(CD_3)_2SO$ or $(CD_3)_2CO$ using TMS as an internal standard. Chemical shift values (δ) are given in ppm and *J* values are given in Hz. Splitting pattern are designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. Mass spectra were recorded on using APCI mode and ion trap analyzer. The high resolution mass spectral (HRMS) data were obtained under ESI ionization mode and TOF analyzer. The infra-red (IR) spectra were recorded on a FT-IR spectrometer in the range 4000-600 cm^{-1} either as neat samples or using KBr for preparing pellets for solid samples. Compounds were routinely checked for their purity on the silica gel GF-254 and visualized under UV at wavelength 254 nm. Melting points were measured with melting point apparatus and were uncorrected. Solvents were removed under rotary vacuum evaporation.

Representative procedure for the one-pot synthesis of 2-styryl-quinolines:

Synthesis of (*E*)-ethyl 4-phenyl-2-styrylquinoline-3-carboxylate 5 (Entry 2, Table 4): To the magnetically stirred mixture of 2-aminobenzophenone **1** (0.49 g, 2.5 mmol) and ethyl acetoacetate **2** (0.33 g, 2.5 mmol, 1 equiv) was added $In(OTf)_3$ (0.14 g, 0.25 mmol, 10 mol%), and the reaction mixture was heated at 100 °C under neat condition. After the complete consumption of 1 (TLC, 15 min), benzaldehyde **3** (0.26 g, 2.5 mmol, 1 equiv) was added and the stirring was continued further for 2 h. The mixture was diluted with ethanol (15 mL) and the resulting supernatant liquid was filtered out. The residue in the flask was washed with ethanol (2 × 5 mL) and in each case the supernatant liquid was filtered out. The combined ethanolic extracts were evaporated to dryness under rotary vacuum evaporation and the residue was recrystallised from ethanol-water (9:1) to obtain analytically pure product (*E*)-ethyl 4-phenyl-2-styrylquinoline-3-carboxylate **5** (0.77 g, 82%) as white solid; mp: 149-152 °C; IR (KBr) ν_{max}: 3415, 2921, 1724, 1276, 1070, 766 cm-1; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) 8.18 (d, *J* = 15.5 Hz, 1H), 8.14 (d, *J* = 0.7 Hz, 1H), 7.81-7.85 (m, 1H), 7.70 (d, *J* = 7.16 Hz, 2H), 7.53-7.60 (m, 5H), 7.35-7.46 (m, 6H), 4.14 (q, *J* = 7.2 Hz, 2H), 0.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 156.1, 144.1, 135.3, 130.9, 129.1, 129.0, 128.7, 128.4, 128.3, 128.2, 127.9, 127.7, 127.5, 127.0, 126.5, 126.4, 125.1, 60.4. 14.2; MS (APCI) m/z: 380.21 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{21}NO_2Na$ 402.1465; Found 402.1463.

The remaining reactions were carried out following this general procedure. The purification was carried out by crystallization in aq. EtOH except the entries 11 and 17 where column chromatography (hexane-EtOAc: 10:1) were used to isolated the desired product. In each occasion, the compounds were characterized (mp, IR, NMR, MS, and HRMS). All of the compounds synthesized under this study [except the (*E*)-Ethyl 2-(4-chlorostyryl)-4-phenylquinoline-3-carboxylate **8**: entry 9, table 3] are new.

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(*E*)-Methyl 4-phenyl-2-styrylquinoline-3-carboxylate (Entry 1, Table 3): Yellow solid (0.73 g, 80%); mp: 157-158 °C; IR (KBr) ν_{max}: 3573, 3005, 1728, 1566, 1394, 1260, 1040, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.20 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 15.6 Hz, 1H), 7.75-7.80 (m, 1H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.61 (dd, *J* = 0.8 Hz & 8.4 Hz, 1H), 7.51-7.56 (m, 3H), 7.41-7.48 (m, 5H), 7.32-7.37 (m, 2H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.3, 155.9, 147.5, 146.2, 144.0, 135.9, 131.1, 129.9, 129.8, 129.5, 129.4, 129.2, 128.3, 128.10, 127.5, 126.4, 126.3, 125.0, 61.3; MS (APCI) m/z: 366.18 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{19}NO_2Na$ 388.1308; Found 388.1302.

(*E*)-Ethyl 6-chloro-4-phenyl-2-styrylquinoline-3-carboxylate (Entry 3, Table 3): Yellow solid (0.84 g, 82%); mp: 143-145 °C; IR (KBr) ν_{max}: 3573, 2988, 1728, 1566, 1447, 1260, 1069, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (dd, *J* = 4.1 Hz & 13.4 Hz, 2H), 7.61-7.68 (m, 3H), 7.50-7.53 (m, 4H), 7.31-7.41 (m, 6H), 4.10 (q, *J* = 7.0 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 151.3, 146.5, 145.9, 136.9, 136.5, 135.1, 132.6, 131.4, 131.2, 129.4, 128.9, 128.8, 128.7, 128.5, 127.7, 127.6, 126.5, 125.2, 124.0, 61.7, 13.7; MS (APCI) m/z: 414.21 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}ClNO_2Na$ 436.1075; Found 436.1075.

(*E*)-Ethyl 2-(4-methylstyryl)-4-phenylquinoline-3-carboxylate (Entry 4, Table 3): White solid (0.79 g, 81%); mp: 141-142 °C; IR (KBr) ν_{max}: 3413, 2925, 1726, 1275, 1069, 764 cm^{-1}; ^1H NMR (400 MHz, $(CDCl_3)$): δ (ppm) 8.13 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 14.7 Hz, 1H), 7.84 (d, *J* = 6.7 Hz, 1H), 7.48-7.60 (m, 7H), 7.38 (t, *J* = 2.5 Hz, 2H), 7.22-7.26 (m, 3H), 4.11 (q, *J* = 7.0 Hz, 2H), 2.34 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.8, 152.1, 148.1, 146.6, 136.5, 136.2, 135.8, 130.3, 129.4, 129.3, 128.7, 128.6, 128.4, 128.2, 127.6, 127.0, 126.6, 126.4, 125.6, 124.4, 61.8, 21.0, 13.6; MS (APCI) *m/z* 394.23 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{23}NO_2Na$ 416.1621; Found 416.1618.

(*E*)-Ethyl 2-(4-methoxystyryl)-4-phenylquinoline-3-carboxylate (Entry 5, Table 3): White solid (0.77 g, 75%); mp: 156-158 °C; IR (KBr) ν_{max}: 2954, 1718, 1510, 1254, 1062, 762 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.09 (s, 1H), 7.99 (d, *J* = 16.0 Hz, 1H), 7.83 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.51 (t, *J* = 16.2 Hz, 5H), 7.35 (d, *J* = 3.7 Hz, 2H), 7.12 (d, *J* = 15.5 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 4.09 (d, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 167.9, 160.6, 150.8, 147.8, 146.5, 136.1, 135.3, 131.5, 129.6, 129.5, 129.2, 128.9, 128.8, 127.6, 127.0, 126.5, 125.2, 121.7, 114.9, 61.8, 55.7, 13.9; MS (APCI) m/z: 410.19 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{23}NO_3Na$ $[M + Na]^+$, 432.1570; Found 432.1572.

(*E*)-Methyl 2-(2-nitrostyryl)-4-phenylquinoline-3-carboxylate (Entry 6, Table 3): White solid (0.88 g, 83%); mp: 185-188 °C; IR (KBr) ν_{max}: 2926, 1721, 1516, 1275, 1066, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.48 (d, *J* = 15.2 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.74-7.81 (m, 2H), 7.59-7.65 (m, 2H), 7.44-7.52 (m, 6H), 7.37-7.39 (m, 2H), 7.31 (d, *J* = 15.7 Hz, 1H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.8, 150.0, 148.5, 148.1, 147.2, 135.7, 133.1, 132.5, 131.5, 130.7, 129.9, 129.5, 129.2, 128.9, 128.3, 127.2, 126.7, 126.5, 125.9, 124.7, 52.3; MS (APCI) m/z: 425.20 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}N_2O_4Na$ 447.1315; Found 447.1312.

(*E*)-Methyl 6-chloro-4-phenyl-2-[4-(trifluoromethyl)styryl]quinoline-3-carboxylate (Entry 7, Table 3): White solid (0.95 g, 79%); mp: 133-134 °C; IR (KBr) ν_{max}: 3005, 1728, 1566, 1478, 1276, 1126, 1067, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.09- 8.12 (m, 2H), 7.63-7.70 (m, 5H), 7.52-7.56 (m, 4H), 7.33-7.37 (m, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.5, 150.6, 146.5, 146.4, 139.8, 135.2, 134.9, 133.0, 131.7, 131.2, 130.6, 130.3, 129.1, 128.9, 127.7, 127.6, 126.6, 126.3, 125.74, 125.70, 125.4, 125.3, 122.7, 52.5; MS (APCI) m/z: 468.10 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{17}ClF_3NO_2Na$ 490.0792; Found 490.0792.

(*E*)-*E*thyl 2-(4-fluorostyryl)-4-phenylquinoline-3-carboxylate (Entry 8, Table 3): White solid (0.81 g, 82%); mp: 147-148 °C; IR (KBr) ν_{max}: 2959, 1723, 1508, 1232, 1066, 764 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) 8.13-8.17 (m, 2H), 7.75-7.86 (m, 3H), 7.52-7.59 (m, 5H), 7.34-7.44 (m, 3H), 7.21 (t, *J* = 8.3 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ (ppm) 168.4, 151.3-148.9 (d, $^1J_{FC}$ = 245 Hz), 147.4, 136.6, 135.6, 133.91-133.88 (d, $^4J_{FC}$ = 3 Hz), 131.6, 130.4-130.3 (d, $^3J_{FC}$ = 8Hz), , 129.5, 129.2, 128.1, 127.9, 127.2, 126.5, 124.9, 116.7-116.5 (d, $^2J_{FC}$ = 22 Hz), 62.1, 14.0; MS (APCI) m/z: 398.24 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd $C_{26}H_{20}FNO_2Na$ 420.1370; Found 420.1368.

(*E*)-Ethyl 2-(4-chlorostyryl)-4-phenylquinoline-3-carboxylate[8] (Entry 9, Table 3): White solid (0.87 g, 84%); mp: 150-152 °C; IR (KBr) ν_{max}: 2926, 1723, 1489, 1216, 1066, 764 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.15 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 15.6 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 3.2 Hz, 4H), 7.50 (d, *J* = 8.3 Hz, 3H), 7.39 (t, *J* = 3.2 Hz, 2H), 7.31 (d, *J* = 15.6 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 0.88 (t, *J* = 7.0 Hz, 3H); MS (APCI) m/z: 414.12 $(M + H)^+$.

(*E*)-Ethyl 2-(4-bromostyryl)-4-phenylquinoline-3-carboxylate (Entry 10, Table 3): White Solid (0.92 g, 81%); mp: 163-165 °C; IR (KBr) ν_{max}: 2926, 1723, 1487, 1233, 1072, 764 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.15 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 15.6 Hz, 1H), 7.87 (t, *J* = 7.5 Hz, 1H), 7.69-7.57 (m, 8H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 3.9 Hz, 2H), 7.33 (d, *J* = 15.6 Hz, 1H), 4.10 (q, *J* = 6.9 Hz, 2H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.3, 156.4, 147.4, 146.1, 145.1, 136.0,130.1, 129.9, 129.5, 129.4, 129.2, 128.3, 128.1, 128.1, 127.9, 127.6, 126.3, 126.0, 125.0, 61.2, 13.6; MS (APCI) m/z: 458.20 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}BrNO_2Na$ 480.0570; Found 480.0572.

(*E*)-Ethyl 2-[2-(furan-2-yl)vinyl]-4-phenylquinoline-3-carboxylate (Entry 11, Table 3): White solid (0.66 g, 72%); mp: 165-166 °C; IR (KBr) ν_{max}: 3447, 2930, 1725, 1545, 1172, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 15.3 Hz, 1H), 7.71-7.75 (m, 1H), 7.56 (d, *J* = 8.4 1H), 7.47-7.53 (m, 4H), 7.39-7.43 (m, 3H), 7.26 (d, *J* =15.3 Hz, 1H), 6.58 (d, *J* = 3.3 Hz, 1H), 6.47- 6.48 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.2, 152.9, 150.8, 148.1, 146.6, 143.3, 135.8, 130.4, 129.5, 129.4, 128.4, 128.2, 127.0, 126.5, 126.4, 125.7, 123.4, 122.4, 112.1, 112.0, 61.5, 13.6; MS (APCI) m/z: 370.18 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{19}NO_3Na$

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392.1257; Found 392.1258.

(*E*)-Methyl 4-phenyl-2-[2-(thiophen-2-yl)vinyl]quinoline-3-carboxylate (Entry 12, Table 3): White solid (0.67 g, 73%); mp: 160-162 °C; IR (KBr) ν_{max}: 3456, 2918, 1723, 1543, 1275, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.08-8.15 (m, 2H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.57 (m, 1H), 7.49-7.52 (m, 4H), 7.32-7.45 (m, 5H), 7.14 (d, *J* = 15.5 Hz, 1H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 151.1, 148.1, 146.8, 139.5, 135.8, 130.5, 130.4, 130.3, 129.5, 129.3, 129.2, 128.5, 128.3, 126.7, 126.6, 126.5, 125.6, 125.5, 125.3, 124.1, 52.3; MS (APCI) m/z: 372.15 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{17}NO_2SNa$ 394.0872; Found 394.0869.

(*E*)-Ethyl 6-chloro-4-phenyl-2-[2-(thiophen-2-yl)vinyl]quinoline-3-carboxylate (Entry 13, Table 3): Yellow solid (0.73 g, 70%); mp: 174-176 °C; IR (KBr) ν_{max}: 2925, 1724, 1576, 1470, 1275, 1123, 1014, 751, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.22 (d, *J* = 15.2 Hz, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 7.65 (dd, *J* = 2.3 Hz & 8.9 Hz, 1H), 7.50-7.53 (m, 4H), 7.35-7.38 (m, 2H), 7.26-7.30 (m, 2H), 7.10 (d, *J* = 15.2 Hz, 1H), 7.04-7.06 (m, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.8, 151.0, 146.5, 145.9, 142.0, 135.1, 132.5, 131.4, 131.0, 129.6, 129.4, 128.9, 128.8, 128.5, 127.9, 127.5, 126.43, 126.39, 125.2, 123.2, 61.7, 13.7; MS (APCI) m/z: 420.08 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{18}ClNO_2SNa$ 442.0639; Found 442.0636.

(*E*)-Ethyl 4-phenyl-2-[2-(pyridin-3-yl)vinyl]quinoline-3-carboxylate (Entry 14, Table 3): White solid (0.66 g, 70%); mp: 154-159 °C; IR (KBr) ν_{max}: 2981, 1723, 1543, 1217, 806 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$): δ (ppm) 8.11 (dd, *J* = 0.7 Hz & 1.6 Hz, 1H), 7.99 (d, *J* = 15.3 Hz, 1H), 7.80- 7.84 (m, 1H), 7.67 (t, *J* = 0.9 Hz, 1H), 7.25-7.58 (m, 6H), 7.40-7.43 (m, 2H), 7.24 (d, *J* = 15.3 Hz, 1H), 6.78 (dd, *J* = 0.3 Hz & 3.2 Hz, 1H), 6.59 (dd, *J* = 1.8 Hz & 3.4 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.1, 154.2, 150.3, 149.7, 148.9, 148.9, 138.1, 135.1, 134.9, 130.2, 129.8, 129.5, 128.7, 128.6, 126.8, 126.0, 125.8, 123.7, 118.8, 60.4, 14.2; MS (APCI) *m/z* 381.21 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{20}N_2O_2Na$ 403.1417; Found 403.1417.

(*E*)-Ethyl 2-{2-(benzo[d][1,3]dioxol-5-yl)vinyl}-4-phenylquinoline-3-carboxylate (Entry 15, Table 3): White solid (0.85 g, 81%); mp: 142-144 °C; IR (KBr) ν_{max}: 2925, 1721, 1488, 1253, 1234, 1038, 803 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.10 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 15.5 Hz, 1H), 7.83 (t, *J* = 6.9 Hz, 1H), 7.46-7.55 (m, 5H), 7.34-7.36 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 15.4 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.07 (s, 2H), 4.09 (q, *J* = 6.7 Hz, 2H), 0.87 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 167.8, 150.8, 148.7, 148.5, 147.8, 146. 6, 136.3, 135.4, 131.5, 130.7, 129.6, 129.5, 129.2, 128.9, 127.6, 127.1, 126.5, 125.3, 123.8, 122.4, 109.1, 106.7, 101.9, 61.8, 13.9; MS (APCI) *m/z* 424.23 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{21}NO_4Na$ 446.1363; Found 446.1361.

(*E*)-Methyl 2-{2-(benzo[d][1,3]dioxol-5-yl)vinyl}-6-chloro-4-phenylquinoline-3-carboxylate (Entry 16, Table 3): Yellow solid (0.89 g, 81%); mp: 175-176 °C; IR (KBr) ν_{max}: 3788, 3573, 3006, 1729, 1562, 1446, 1255, 1040, 750 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (d, *J* = 9.0 Hz, 1H), 8.00 (d, *J* = 15.4 Hz, 1H), 7.65 (dd, *J* = 2.3 Hz & *J* = 9.0 Hz, 1H), 7.50-7.52 (m, 4H), 7.35-7.37 (m, 2H), 7.07-7.14 (m, 3H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.00 (s, 2H), 3.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.6, 151.4, 148.5, 148.2, 146.6, 146.0, 136.7, 135.1, 132.4, 131.5, 131.05, 130.93, 129.2, 128.8, 128.5, 126.2, 125.2, 123.5, 122.0, 108.5, 106.3, 101.4, 52.4; MS (APCI) m/z 444.21 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{18}ClNO_4Na$ 466.0817; Found 466.0820.

Ethyl 6-chloro-4-phenyl-2-[(1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl]quinoline-3-carboxylate (Entry 17, Table 3): Yellow solid (0.83 g, 76%); mp: 130-132 °C; IR (KBr) ν_{max}: 1733, 1564, 1260, 1219, 1067, 750, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (d, *J* = 9.0 Hz, 1H), 7.92 (dd, *J* = 10.8 Hz & 14.7 Hz, 1H), 7.65 (dd, *J* = 2.3 Hz & 9.0 Hz, 1H), 7.48-7.54 (m, 6H), 7.34-7.37 (m, 4H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.06 (q, *J* = 10.9 Hz & 15.7 Hz, 1H), 6.85-6.95 (m, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 151.4, 146.6, 145.8, 137.3, 137.0, 135.1, 132.4, 131.4, 131.1, 129.4, 128.8, 128.7, 128.5, 128.4, 128.3, 127.7, 127.6, 126.9, 126.3, 125.2, 61.7, 13.6; MS (APCI) m/z 554.21 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{22}ClNO_2Na^+$ $[M + Na^+]$, 462.1231; Found 462.1232.

Representative procedure for large scale synthesis of 2-styrylquinolines and recovery/reuse of $In(OTf)_3$ during the one-pot synthesis of 2-styryl-quinolines. Synthesis of (*E*)-ethyl 4-phenyl-2-styrylquinoline-3-carboxylate 5: To the magnetically stirred mixture of **1** (4.92 g, 25 mmol,) and **2** (3.25 g, 25 mmol, 1 equiv) was added $In(OTf)_3$ (1.40 g, 10 mol%) and the reaction mixture was heated at 100 °C under neat. After the complete consumption of **1** (TLC, 30 min), **3** (2.65 g, 25 mmol, 1 equiv) was added and the stirring was continued further for 3 h. The mixture was diluted with ethanol (100 mL) and the resulting supernatant liquid was filtered out. The solid residue that remained in the flask was washed with ethanol (2 × 10 mL). The combined ethanolic extracts were evaporated to dryness under rotary vacuum evaporation and the crude product was recrystallised from ethanol-water (9:1) to obtain analytically pure product **5** (7.77 g, 82%) as white solid. The solid residue (catalyst) that remained in the flask was collected and dried to obtain the recovered $In(OTf)_3$ (1.26 g, 90 %). The reaction was repeated with **1**, **2** and **3** at 5 mmol, 2.5 mmol, and 1 mmol scales in the presence of the recovered $In(OTf)_3$ (280 mg, 140 mg, and 57 mg, respectively) to afforded **5** in 80, 76, and 70% yields, respectively.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Spectral data of all compounds, scanned spectra (^1H of all compounds and ^{13}C of unknown compounds). See DOI: 10.1039/b000000x/

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$In(OTf)_3$-Catalyzed synthesis of 2-styryl quinolines: Scope and limitations of metal Lewis acids for tandem Friedländer annulation-Knoevenagel condensation

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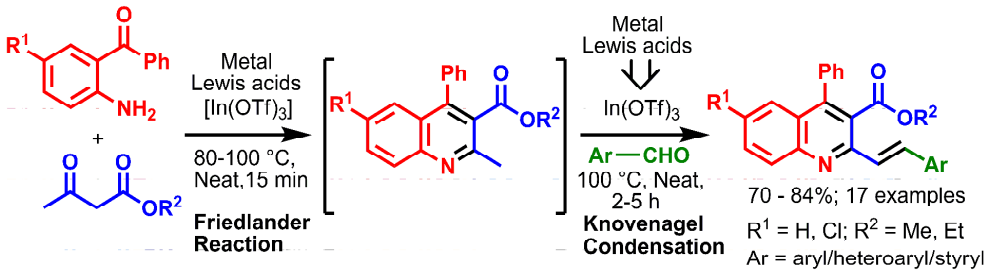

Investigation of metal Lewis acids for one-pot tandem Friedländer annulation-Knoevenagel condensation and exploration of $In(OTf)_3$ for synthesis of 2-styryl quinolines

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