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# Friedländer annulation: Scope and limitations of metal salt Lewis acid catalysts in selectivity control for the synthesis of functionalised quinolines

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The scope and limitations of metal salt Lewis acid catalysts were examined for the selectivity control for the formation of Friedländer and non-Friedländer product during the reaction involving 2-aminobenzophenone and ethyl acetoacetate. From a pool of metal halides, tetrafluoroborates, perchlorates, and triflates used as catalyst,  $In(OTf)_3$  emerged as the most effective catalyst for selective/exclusive formation of the Friedländer product. The generality of the  $In(OTf)_3$ -catalysed Friedländer reaction was demonstrated by the reaction of differently substituted 2-aminoarylketones with various carbonyl compounds containing active methylene group (e.g.,  $\beta$ -ketoesters, cyclic/acyclic  $\beta$ -diketones, cyclic/acylic ketones, and aryl/heteroaryl methyl ketones) under solvent-free conditions affording the desired quinolines in 75-92% yields.

# Introduction

The broad spectrum of biological activities of quinolines in diverse therapeutic areas<sup>1</sup> has generated perpetual interest to develop newer synthetic methods for the preparation of this privileged class of compounds.

Friedländer annulation, the acid or base-catalysed cyclocondensation of 2-amino-substituted aromatic aldehydes/ketones with carbonyl derivatives containing activemethylene group, is the most general and straight forward method (Scheme 1) for the synthesis of quinolines. Consequently, development of newer variation of the Friedländer reaction continues to draw attention of the synthetic organic/medicinal chemists.<sup>2</sup> Different Brønsted<sup>3</sup> and Lewis<sup>4</sup> acids have been used as catalysts offering advantages over the thermal processes<sup>5</sup> or the base-catalysed reactions.<sup>6</sup> However, in some of these methodologies the ketones (e.g., 2aminobenzophenone) fail to react with ethyl acetoacetate to afford the desired quinoline.<sup>7</sup>



Scheme 1. Friedländer annulation reaction.

The selectivity control<sup>8</sup> often becomes a bottleneck in organic synthesis. Such a situation is envisaged during the cyclocondensation of 2-aminoaryl ketones with  $\beta$ -ketoesters

that would offer a convenient approach for the preparation of quinolines. The metal salt Lewis acid catalysed reaction of 2-aminobenzophenone (1) and ethyl acetoacetate (2) (Scheme 2) may pose the selectivity problem due to the competitive formation of the Friedländer product **3a** and the non-Friedländer product **3b**. This issue on selectivity problem remained unaddressed so far.



Scheme 2. Competitive formation of the Friedländer (3a) and non-Friedländer (3b) products during the reaction of 1 with 2.

The present work aims to investigate the selectivity control in the presence of various metal salt Lewis acid catalysts during the cyclocondensation of **1** with **2** and subsequent assessment of the scope and limitations of the metal salt Lewis acids as catalysts for a generalized synthesis of functionalised quinolines.

# **Results/Discussion**

The Friedländer annulation to form quinolines may proceed via two pathways: (i) Schiff base formation<sup>9</sup> followed by intramolecular Knoevenagel condensation of the aryl ketone with the active methylene group of the intermediate Schiff base,<sup>10</sup> (ii) Knoevenagel condensation of the aryl ketone with the active methylene group of the reacting partner followed by intramolecular imine formation<sup>11</sup> (Scheme 3). The un-catalysed process may lead to the formation of the non-Friedländer product<sup>7,12</sup> via initial amide formation by the reaction of the amino group with the ester carbonyl of ethyl acetoacetate

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followed by intramolecular Knoevenagel condensation (Scheme 4). The use of base catalysts also direct the reaction towards the formation of the non-Friedländer product.<sup>7,13</sup> The recent report<sup>14</sup> on Friedländer reaction without using any catalyst, however, is associated with the hydrolytic decomposition of the ester functionality in the final product and requires heating in a solvent at high temperature (~140 °C) for prolonged period (~24 h).

Thus, the selectivity of formation of the Friedländer versus the non-Friedländer product would depend on the effectiveness of the metal salt Lewis acids.



Scheme 3. Mechanistic pathways of metal salt Lewis acid (LA) catalysed Friedländer annulation to from guinolines.

#### Non-Friedlander product formation

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Scheme 4. Mechanistic pathway of the un-catalysed reaction of 2-aminoaryl ketones with active methylene compounds leading to the formation of the non-Friedländer product.

As metal salt of a strong protic acid should be a strong Lewis acid, metal triflates could be ideal catalyst as TfOH is the strongest protic acid  $(H_0 = -14.1)$ .<sup>15</sup> However, the possibility of ligand exchange of metal triflates during the progress of the reaction often raises query as to the nature of the actual catalytic species/agent. Although HNTf<sub>2</sub> is a weaker Brønsted acid than TfOH<sup>16</sup> and ligand exchange is usually not observed with metal triflimides,<sup>17</sup> the high cost and lack of commercially availability make metal triflimides less popular. Although a few metal triflates have been used for guinoline synthesis via Friedländer annulation<sup>4h-j</sup> the issue of selectivity control for the Friedländer versus non-Friedländer product formation remained unaddressed and in some cases<sup>4i</sup> the reaction was performed under microwave irradiation. Hence, a model reaction (Scheme 2) involving 1 and 2 was performed under the catalytic influence of various metal triflates under solvent free conditions at 100 °C (oil bath). The selection of solventfree conditions was made in order to avoid any influence of solvent properties on the selectivity control to form 3a and 3b. Among Zn, Mg, Er, In, Cu, Sc, Gd, Ho, Dy, Nd, Al, Ag, La, and Sm-triflates tested, the most promising results were obtained with Zn(OTf)<sub>2</sub>, In(OTf)<sub>3</sub>, Gd(OTf)<sub>3</sub>, Dy(OTf)<sub>3</sub>, and Al(OTf)<sub>3</sub> affording 3a in >80% yield with 100% selectivity. The overall catalytic potential of the metal triflates for the selective formation of **3a** follows the order  $In(OTf)_3 > Zn(OTf)_2 \sim$  $Gd(OTf)_3 \sim Dy(OTf)_3 \sim Al(OTf)_3 \sim Er(OTf)_3 > Sc(OTf)_3$ 

 $Sm(OTf)_2 > Mg(OTf)_2 \sim Cu(OTf)_2 \sim Nd(OTf)_3 \sim La(OTf)_3 \sim$  $Ho(OTf)_3 > AgOTf.$ 

As the metal perchlorates<sup>9a,b,18</sup> appear to be the next best effective electrophilic activating agents it was next planned to investigate the use of metal perchlorates.<sup>19</sup> Among Zn, Fe, Cu, Zr, In, Bi, Al, Mg, and Li-perchlorates the use of Zn(ClO<sub>4</sub>)<sub>2</sub>·xH<sub>2</sub>O provided the best result (3a was obtained in 82% yield with 100% selectivity) followed by  $Mg(ClO_4)_2 \cdot 6H_2O$  and  $Cu(ClO_4)_2 \cdot 6H_2O$ . In case of LiClO<sub>4</sub>, a reversal of selectivity was observed in forming 3a and 3b in a ratio of 40:60. The relative catalytic activity of the metal perchlorates in controlling 3a versus **3b** selectivity is found to be in the order  $Zn(ClO_4)_2 \cdot xH_2O$ >  $Mg(CIO_4)_2 \cdot 6H_2O$  >  $Cu(CIO_4)_2 \cdot 6H_2O$  >  $In(CIO_4)_3 \cdot 6H_2O$  >  $ZrO(ClO_4)_2 \cdot xH_2O > BiOClO_4 \cdot xH_2O \sim Fe(ClO_4)_3 \cdot xH_2O$ >  $AI(CIO_4)_3 \cdot 9H_2O > LiCIO_4.$ 

Metal tetrafluoroborates, derived from weaker Brønsted acid such as HBF<sub>4</sub>, are expected to be milder Lewis acid catalysts and are known to catalyze various organic reactions.<sup>20</sup> Therefore, various metal tetrafluoroborates (e.g., Zn, Fe, Ag, Cu, and Co-tetrafluoroborates) were used to promote the cyclocondensation of 1 with 2 and the best result was obtained with Zn(BF<sub>4</sub>)<sub>2</sub> affording 3a in 91% yield with 100% selectivity. The overall catalytic potential of the metal tetrafluoroborates towards the selective formation of 3a follows the order  $Zn(BF_4)_2 > AgBF_4 \sim Cu(BF_4)_2 > Co(BF_4)_2 >$  $Fe(BF_4)_2 \cdot xH_2O.$ 

A few commonly used metal halides were also investigated to determine their scope and limitations as catalysts for Friedländer annulation reaction. Among the different metal halides screened (In, Zr, Ga, Nb, Hf), the best result was obtained with HfCl<sub>4</sub> affording 3a in 84% yield with 100% selectivity. However, the use of CeCl<sub>3</sub>·7H<sub>2</sub>O under microwave irradiation has been reported to form the non-Friedländer product 3b.21

Table 1. The assessment of the catalytic potential of various metal salt Lewis acid catalysts for the selectivity control during the reaction of 1 and 2 to form 3a and 3b.ª

$\bigcirc$	O Ph + ↓	OEt Metal Lewis acid (10 mol%) Neat, 100 °C, 1h	Ph O	`OEt +	Ph O N H		
1		2	3a		3b		
Entry	Catalyst	Yield (%) <sup>b</sup>	Selectiv	ˈity <sup>c</sup>			
		(3a + 3b)	3a	3b			
1	None	45	traces	100			
		Metal trifla	ites				
2	Zn(OTf) <sub>2</sub>	81	100	00			
3	Mg(OTf) <sub>2</sub>	80	90	10			
4	Er(OTf) <sub>3</sub>	82	98	00			
5	In(OTf) <sub>3</sub>	90	100	00			
6	Cu(OTf) <sub>2</sub>	75	90	10			
7	Sc(OTf) <sub>3</sub>	83	94	06			
8	Gd(OTf) <sub>3</sub>	85	100	00			
9	Sm(OTf) <sub>2</sub>	81	94	06			
10	Dy(OTf)₃	84	100	00			
11	Nd(OTf) <sub>3</sub>	80	90	10			
12	Al(OTf)₃	81	100	00			
13	AgOTf	72	70	30			
14	La(OTf) <sub>3</sub>	77	90	10			
15	Ho(OTf) <sub>3</sub>	85	90	10			
	Metal perchlorates						

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16	Zn(ClO <sub>4</sub> ) <sub>2</sub> ·xH <sub>2</sub> O	82	100	00
17	Fe(ClO <sub>4</sub> ) <sub>3</sub> ·xH <sub>2</sub> O	72	70	30
18	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	81	90	10
19	ZrO(CIO <sub>4</sub> ) <sub>2</sub> ·xH <sub>2</sub> O	70	75	25
20	In(CIO <sub>4</sub> ) <sub>3</sub> ·6H <sub>2</sub> O	76	85	15
21	BiOClO <sub>4</sub> ·xH <sub>2</sub> O	65	75	25
22	AI(CIO <sub>4</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	65	60	40
23	Mg(CIO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	82	95	05
24	LiCIO <sub>4</sub>	62	40	60
		Metal tetrafluorobora	ites	
25	$Zn(BF_4)_2$	91	100	00
26	Fe(BF <sub>4</sub> ) <sub>2</sub> ·xH <sub>2</sub> O	84	70	30
27	AgBF₄	72	85	15
28	Cu(BF <sub>4</sub> ) <sub>2</sub>	78	85	15
29	Co(BF <sub>4</sub> ) <sub>2</sub>	69	75	25
		Metal halides		
30	InF₃	72	90	10
31	InCl <sub>3</sub>	78	98	00
32	InBr <sub>3</sub>	70	85	15
33	InI <sub>3</sub>	72	82	18
34	ZrCl <sub>4</sub>	69	85	15
35	GaCl <sub>3</sub>	70	84	16
36	NbCl <sub>5</sub>	63	70	30
37	HfCl₄	84	100	00

<sup>a</sup>1 (0.197 g, 1 mmol) was treated with 2 (0.13 g, 1 mmol, 1 equiv) in the presence of different metal salt Lewis acid catalysts (10 mol%) under neat conditions at 100 °C for 1 h. <sup>b</sup>Isolated yield of the products (3a and 3b). <sup>c</sup>Selectivity (ratio of 3a and 3b as determined by GC-MS).

However, based on the above results it is difficult to make a clear cut selection of the most effective catalyst as in each category some metal salt Lewis acids exhibited promising selectivity towards 3a with excellent yields.

Thus, the selected panel of metal salt Lewis acid catalysts [Zn(BF<sub>4</sub>)<sub>2</sub>, Zn(ClO<sub>4</sub>)<sub>2</sub>·xH<sub>2</sub>O, Mg(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O, Zn(OTf)<sub>2</sub>, Mg(OTf)<sub>2</sub>, Er(OTf)<sub>3</sub>, In(OTf)<sub>3</sub>, Cu(OTf)<sub>2</sub>, Sm(OTf)<sub>2</sub>, Gd(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, Gd(OTf)<sub>3</sub>, Nd(OTf)<sub>3</sub>, Al(OTf)<sub>3</sub>, Dy(OTf)<sub>3</sub>, HfCl<sub>4</sub>] were subjected to different reaction conditions with variation of the reaction time such as (i) 100 °C for 60 min, (ii) 100 °C for 30 min and (iii) 100 °C for 15 min to distinguish their catalytic potential (Table 2). This led to the selection of  $Er(OTf)_3$ ,  $In(OTf)_3$  and  $Sc(OTf)_3$  as the three best catalysts with comparable catalytic activity. Further experiments were designed and executed to differentiate the catalytic potential of Er(OTf)<sub>3</sub>, In(OTf)<sub>3</sub> and Sc(OTf)<sub>3</sub> under different operating conditions such as (i) 80 °C for 30 min, (ii) 80 °C for 15 min, (iii) 80 °C for 10 min, (iv) 60 °C for 30 min, (v) 50 °C for 15 min using 10 mol% of catalyst loading and (vi) 80 °C for 15 min using 5 mol% of catalyst loading. However, the results reflected comparable catalytic efficiency of these three triflates. For further use,  $In(OTf)_3^{22}$ was considered based on its lower cost compared to that of Er(OTf)<sub>3</sub> and Sc(OTf)<sub>3</sub>.+

Table 2. The assessment of catalytic potential of a few selected metal salt Lewis acid catalysts of Table 1, for the Friedländer synthesis of 3a.ª

Ent	ry	Catalyst	Time (min)	Temp (°C)	Yield (%) <sup>b</sup>
1	Zn(B	F <sub>4</sub> ) <sub>2</sub>	60	100	100
2			30	100	62
3			15	100	39
4	Zn(C	IO <sub>4</sub> ) <sub>2</sub> ·xH <sub>2</sub> O	60	100	100
5			30	100	73
6			15	100	55
7	Mg(0	CIO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	60	100	96
8			30	100	62

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55<sub>0</sub>

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9 10	Zn(OTf) <sub>2</sub>	15	188	100
11		30	100	72
12		15	100	61
13	Mg(OTf) <sub>2</sub>	60	100	94
14		30	100	56
15		15	100	34
16	Er(OTf)₃	60	100	96
17		30	100	96
18		15	100	95
19	In(OTf)₃	60	100	100
20		30	100	100
21		15	100	100
22	Cu(OTf) <sub>2</sub>	60	100	92
23		30	100	90
24		15	100	51
25	Sc(OTf)₃	60	100	94
26		30	100	95
27		15	100	95
28	Gd(OTf)₃	60	100	99
29		30	100	72
30		15	100	51
31	Sm(OTf)₂	60	100	94
32		30	100	62
33		15	100	35
34	Dy(OTf)₃	60	100	99
35		30	100	61
36		15	100	40
37	Nd(OTf) <sub>3</sub>	60	100	92
38		30	100	65
39		15	100	43
40	Al(OTf) <sub>3</sub>	60	100	98
41	( )-	30	100	61
42		15	100	41
43	HfCl₄	60	100	99
44		30	100	56
45		15	100	31
46	InCl <sub>3</sub>	60	100	98
47		30	100	64
48		15	100	46
49	In(OTf) <sub>3</sub>	10	100	72
50	Sc(OTf) <sub>3</sub>	10	100	75
51	Er(OTf) <sub>3</sub>	10	100	70
52	In(OTf) <sub>3</sub>	30	80	100
53	Sc(OTf)₃	30	80	98
54	Er(OTf) <sub>3</sub>	30	80	95
55	In(OTf) <sub>3</sub>	10	80	70
56	Sc(OTf) <sub>3</sub>	10	80	68
57	Er(OTf) <sub>3</sub>	10	80	67
58	In(OTf) <sub>3</sub>	15	80	100
59	Sc(OTf) <sub>3</sub>	15	80	96
60	Er(OTf) <sub>3</sub>	15	80	95
61	In(OTf) <sub>3</sub>	30	60	50
62	Sc(OTf) <sub>3</sub>	30	60	45
63	Er(OTf) <sub>3</sub>	30	60	40
64	In(OTf) <sub>3</sub>	15	50	35
65	Sc(OTf) <sub>3</sub>	15	50	32
66	Er(OTf) <sub>3</sub>	15	50	32
67	In(OTf) <sub>3</sub>	15	80	98 <sup>c</sup>
68	Sc(OTf) <sub>3</sub>	15	80	95 <sup>c</sup>
69	Er(OTf)₃	15	80	98 <sup>c</sup>

<sup>a</sup>1 (0.197 g, 1 mmol) was treated with 2 (0.13 g, 1 mmol, 1 equiv) in the presence of different metal salt Lewis acid catalysts (10 mol%) under neat conditions at different variation of the reaction time and temp. <sup>b</sup>Yield of 3a (GC-MS). <sup>c</sup>The reaction was carried out using 5 mol% of the catalyst.

The effect of various solvents (Table 3) was also evaluated on the progress of In(OTf)<sub>3</sub> catalyzed Friedländer annulation to form 3a. The reaction works best under neat conditions (100%; GC-MS) and the next best results were obtained in EtOH (82%; GC-MS) and MeCN (71%; GC-MS). The use of EtOH afforded comparable yield (96%; GC-MS, 45 min) but required longer

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Neat

Neat

EtOH

EtOH

EtOH

DMF

THF

PhMe

PhMe

PhMe

PhMe

PhMe

PhMe<sup>1</sup>

PhMe<sup>1</sup>

PhMe

**Xylene** 

Xylene

**Xylene** 

**Xvlene** 

**Xylene** 

**Xylene** 

**Xylene** 

Xvlene<sup>6</sup>

Xvlene<sup>6</sup>

Xylene<sup>c</sup>

Xvlene<sup>6</sup>

DMSO

80

rt

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140

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110

110

time. The use of non-polar solvent such as PhMe afforded poor result (entry 6). However, contrary to the recent report<sup>14</sup> on catalyst-free quinoline synthesis that led to the formation of the corresponding carboxylic acid due to hydrolytic decomposition of the final product, the In(OTf)<sub>3</sub> catalyzed reaction under the present study afforded the desired quinoline ester. Thus, experiments were performed in using non-polar solvents such as PhMe and xylene in the presence and absence of In(OTf)<sub>3</sub> under different variation of the reaction temperature and time (entries 6-26, table 3). No product formation was observed when the reaction was performed in toluene/xylene at 80-140 °C (oil bath) for 1 h under catalyst-free conditions (entries 10, 12, 21, 23, and 25, table 3). However, in concurrence with the literature report<sup>14</sup> the carboxylic acid 4 was formed (due to hydrolytic decomposition of 3a) when the reaction was performed in toluene/xylene at 80-140 °C (oil bath) for 24 h in the absence of catalyst (entries 11, 13, 22, 24 and 26, table 3). In sharp contrast to these observations, when the reaction was performed in toluene/xylene 80-140 °C (oil bath) in the presence of In(OTf)<sub>3</sub> (5 mol%) the desired ester 3a was formed (entries 6-9 and 14-20, table 3). These results clearly demonstrate that the use of In(OTf)<sub>3</sub> as the catalyst offers the following distinct advantages: (i) accelerates the condensation to form the Friedländer product 3a and (ii) suppresses the hydrolytic decomposition of 3a to the corresponding carboxylic acid 4.

Table 3. The effect of the reaction medium on the In(OTf)<sub>3</sub>-catalysed Friedländer annulation to form 3a/4.ª

Ni 1	Ph + 4	Solv <u>with/witho</u> OEt Temp,	ent, u <u>t In(OTf)<sub>3</sub> </u> ►   Time	$ \begin{array}{c} Ph & O \\ OEt \\ N \\ 3a \\ \end{array} $ $ \begin{array}{c} Ph & O \\ Ph & O \\ Ph & O \\ OH \\ OH \\ A \\ 4 \\ \end{array} $
Entry	Solvent	Temp (°C)	Time (h)	Yield (%) <sup>b</sup>

15 min

15 min

45 min

15 min

15 min

15 min

15 min

15 min

24

24

24

24

24

1

24

24

15 min

3a

100

65

82

96

85

46

65

64

32

43

35

48

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00

00

40

28

42

34

46

38

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49 (45)<sup>e</sup>

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37 (30)<sup>d</sup>

42 (40)<sup>d</sup>

43 (40)<sup>d</sup>

65 (62)<sup>d</sup>

able	4.	In(OTf)₃-Catalysed	Friedländer	annulations	to	synthesise
unctio	naliz	zed auinolines. <sup>a</sup>				

table acetyl	4), 2-acetylthiopher furan (entry 22, table	ne (entry 4).	21,	table	4),	and	2-
<b>Table</b> functio	<ol> <li>In(OTf)₃-Catalysed nalized quinolines.<sup>a</sup></li> </ol>	Friedländer	annula	itions	to	synthe	sise
×	$\begin{pmatrix} R^1 \\ NH_2 \end{pmatrix} + O \begin{pmatrix} R^2 \\ R^3 \end{pmatrix}$	In(OTf) <sub>3</sub> (5 n Neat, 80 °	nol%) °C ►	×	F	1 R <sup>2</sup> R <sup>2</sup>	
Entry	Product	Tir	ne (min	) Yield	d (%) <sup>b</sup>		
1 2 3 4 5 6 7 8 9 10 11	$\begin{array}{c} R^{1} & O \\ X = H; R^{1} = Ph; R^{2} = OEt \\ X = H; R^{1} = Ph; R^{2} = OMe \\ X = H; R^{1} = Ph; R^{2} = OMe \\ X = CI; R^{1} = Ph; R^{2} = OEt \\ X = CI; R^{1} = Ph; R^{2} = OEt \\ X = H; R^{1} = Ph; R^{2} = OEt \\ X = H; R^{1} = Ph; R^{2} = OEt \\ X = CI; R^{1} = Ph; R^{2} = Ph \\ X = CI; R^{1} = Ph; R^{2} = Ph \\ X = CI; R^{1} = Ph; R^{2} = Ph \\ X = CI; R^{1} = Ph; R^{2} = Ph \\ X = H; R^{1} = Ph; R^{2} = Ph \\ X = H; R^{1} = Ph; R^{2} = Ph \\ X = H; R^{1} = Ph; R^{2} = Ph \\ X = H; R^{1} = Me; R^{2} = O^{4}B \\ Ph & O \\ Ph & O \\ \end{array}$	9 1	15 15 20 30 20 15 20 15 20 20	92 90 88 85 83 87 81 84 80 78			
12 13			25 30	82 81			

<u>28</u>	Xylene <sup>c</sup> Xylene <sup>c</sup>	148	1 24	88	00 71 (68
30	MeCN	80	15 min	71	00
31	MeCN	80	45 min	81	00
32	MeCN	rt	2	90	00
33	Water	80	15 min	24	00
34	DCE	80	15 min	68	00

<sup>a</sup> 1 (0.197 g, 1 mmol) was treated with 2 (0.13 g, 1 mmol, 1 equiv) in the presence of  $\ln(OTf)_3$  (5 mol%) (except for entries 10-13, and 21-26) in different solvent (5 mL) at the indicated temperature (oil bath) for the stipulated time. <sup>b</sup> The GC-MS yield of 3a and 4 unless otherwise mentioned. <sup>c</sup>The reaction was performed in the absence of the catalyst.<sup>d</sup> The figure in the parenthesis is the isolated yield of 4. <sup>e</sup> The figure in the parenthesis is the isolated yield of 3a.

The catalytic potential of In(OTf)<sub>3</sub> was elaborated for the

generalized Friedländer reaction with different variations of

the substrates to prepare diversified quinolines in excellent

yields within short period of time (Table 4). The reactions

proceeded smoothly with different  $\beta$ -ketoesters such as

methyl acetoacetate, ethyl acetoacetate and <sup>t-</sup>butyl

acetoacetate (entries 1-5, table 4). The reactions were

compatible with acyclic diketones (entries 2-11, 23, table 4) as

well as cyclic diketones (entries 12-15, table 4). The

methodology was generalized with respect to cyclic ketones

such as cyclopentanone, cyclohexanone, cycloheptanone and

cyclooctanone, 4-methylcyclohexanone (entries 16-19, 24,

table 4) and acyclic ketone such as acetophenone (entry 20,

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<sup>a</sup>2-Aminoketone (2.5 mmol) was treated with  $\beta$ -ketoester/ $\beta$ -diketone or ketone (2.5 mmol, 1 equiv) in the presence of In(OTf)<sub>3</sub> (5 mol%) under neat conditions at 80 °C for stipulated time. <sup>b</sup>Isolated yield of product.

The distinct advantages of  $In(OTf)_3$  over the reported catalysts with respect to (i) selective/exclusive formation of the Friedländer product **3a** and (ii) improved yield, could be drawn through the results (Table 5) of the cyclocondensation reaction of **1** with **2** performed under similar experimental conditions.

Table 5. The comparison of the efficiency of  $ln(OTf)_3$  with the reported catalysts during the reaction of 1 with 2 for the formation of 3a.<sup>a</sup>

Ent	try Catalyst	Yield (%) <sup>b,c</sup>	Lit. Ref.	
1	Sulfamic acid	79	3a	
2	SnCl <sub>2</sub> •2H <sub>2</sub> O	00	4e	
3	Nd(NO <sub>3</sub> ) <sub>3</sub> •6H <sub>2</sub> O	00	4d	
4	<i>o</i> -TsOH	43 (11)	10a	

<sup>a</sup>**1** (0.197 g, 1 mmol) was treated with **2** (0.13 g, 1 mmol, 1 equiv) in the presence of different catalysts (5 mol%) under neat conditions at 80 °C for 15 min. <sup>b</sup>Isolated yield of the Friendlander product **3a**. <sup>c</sup>The figure in the parenthesis is the yield of the non-Friendlander product **3b**.

# Conclusions

The present work describes the scope and limitations of various metal salt Lewis acids (e.g., metal halides, tetrafluoroborates, perchlorates, and triflates) as catalysts for the selectivity control for the formation of the Friedländer and the non-Friedländer products during the reaction of 2-aminobenzophenone with ethyl acetoacetate. These led to the finding of  $In(OTf)_3$  as the most effective catalyst for selective formation of the Friedländer product. The general applicability of  $In(OTf)_3$  as a catalyst for Friedländer quinoline synthesis has been established during the condensation of substituted 2-aminoarylketones with different carbonyl compounds bearing the active methylene group such as  $\beta$ -ketoesters, cyclic/acyclic  $\beta$ -diketones, cyclic/acylic ketones, and aryl/heteroaryl methyl ketones leading to the formation of the desired quinolines in 75-92% yields under solvent-free conditions.

# **Experimental section**

#### General remarks:

The glasswares used were 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 TLC experiments were performed on silica gel GF-254 and visualized under UV at 254 nm. Evaporation of solvent was performed at reduced pressure using a rotary evaporator. Melting points were measured using a melting point apparatus and were uncorrected. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a 400 MHz NMR spectrometer in CDCl<sub>3</sub>/CD<sub>3</sub>OD/(CD<sub>3</sub>)<sub>2</sub>SO with residual undeuterated solvent (CHCl<sub>3</sub>: 7.26/77.0)/(CH<sub>3</sub>OH: 3.31/49.0)/[(CH<sub>3</sub>)<sub>2</sub>SO: 2.50/39.52] using Me<sub>4</sub>Si as an internal standard. The chemical shift ( $\delta$ ) values are given in ppm and J values are given in Hz. The <sup>13</sup>C NMR spectra were fully decoupled and were referenced to the residual solvent signal peak. Splitting pattern were designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; dt, doublet of triplet and m, multiplet. The mass spectra (MS) were recorded under atmospheric pressure chemical ionization (APCI) and electro spray ionization (ESI). The high resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI). The infra-red (IR) spectra were recorded in the range of 4000-600 cm<sup>-1</sup> as KBr pellets for all solid samples.

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# ARTICLE Procedures

# Selectivity in the formation of 3a and 3b during the various metal salt Lewis acid catalysed reaction of 1 with 2 (Table 1): Synthesis of authentic sample of ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3a).<sup>3a</sup>

The authentic sample of 3a was prepared with minor modification of reported literature method. The mixture of 2aminobenzophenone 1 (0.197 g, 1 mmol), ethyl acetoacetate 2 (0.19 g, 1.5 mmol, 0.19 mL), and sulfamic acid (0.005 g, 1 mmol, 5 mol%) was taken in a round-bottom flask (10 mL) and placed in preheated oil bath at 70 °C (bath temperature) under magnetic stirring for 45 min. After completion of the reaction (45 min, TLC), the mixture was cooled to rt and the residue was extracted with EtOAc ( $3 \times 1 \text{ mL}$ ) and the combined EtOAc extracts were concentrated under reduced pressure. The crude product was adsorbed on silica gel (500 mg, 230-400 mesh size), charged on to a flash chromatography column of silica-gel (2.5 g, 230-400 mesh size), and eluted with hexane-EtOAc (98:2) to obtain analytically pure ethyl 2-methyl-4phenylquinoline-3-carboxylate (3a) (0.23 g, 81 %) as yellow solid; mp: 98-100 °C (lit<sup>3a</sup> 97 °C); IR (KBr) v<sub>max</sub>: 3054, 2976, 1715, 1402, 1236, 1077 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ (ppm) 8.08 (dd, J = 8.5 Hz and 0.3 Hz, 1H), 7.68-7.73 (m, 1H), 7.57 (dd, J = 8.4 Hz and 0.9 Hz, 1H), 7.46-7.49 (m, 3H), 7.39-7.43 (m, 1H), 7.36-7.37 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 2.79 (s, 3H), 0.95 (t, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 168.5, 154.6, 147.7, 146.2, 135.8, 130.3, 129.4, 128.9, 128.5, 128.2, 127.4, 126.5, 126.4, 125.2, 76.7-77.3 (t, CHCl<sub>3</sub>), 61.3, 23.8, 13.6; MS (APCI) *m/z* 292.23 (M+H)<sup>+</sup>.

# Synthesis of authentic sample of 3-acetyl-4-phenylquinolin-2(1*H*)-one (3b).<sup>12</sup>

A solution of 1 (0.49 g, 2.5 mmol) and 2 (0.66 g, 5 mmol, 0.65 mL) was heated under reflux for 4 h. The reaction mixture was cooled and poured slowly, with stirring, into ice-cold water (60 mL). The resulting suspension was allowed to stand under ice bath until the gummy precipitate becomes solid, after which the crude product was collected, washed with water, and recrystallized from aq. EtOH to afford analytically pure 3acetyl-4-phenylquinolin-2(1H)-one (3b) (400 mg, 61%) as offwhite needles; mp: 255-258 °C, (lit<sup>12</sup> 256-258 °C); IR (KBr) v<sub>max</sub>: 3105, 2988, 1830, 1642, 1325, 1281, 1188, 805 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ (ppm) 7.55-7.60 (m, 1H), 7.49-7.52 (m, 3H), 7.41 (d, J = 8.16, 1H), 7.29-7.33 (m, 2H), 7.15-7.22 (m, 2H), 3.30-3.31 (m, MeOH), 2.20 (S, 3H); <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD): δ (ppm): 202.6, 160.2, 148.9, 138.3, 134.2, 132.7, 131.3, 128.8, 128.7, 128.3, 127.3, 122.7, 119.7, 115.5, 46.9-48.2 (septet, MeOH), 30.4; MS (APCI) *m/z* 264.10 (M+H)<sup>+</sup>.

# Representative procedure for assessment of selectivity of formation of 3a and 3b.

To the magnetically stirred mixture of **1** (0.197 g, 1 mmol) and **2** (0.13 g, 1 mmol, 0.13 mL) was added the metal salt Lewis acid catalyst (10 mol%) under neat condition at 100 °C. After completion of the reaction (1 h, TLC) the mixture was cooled to rt and extracted with EtOAc ( $3 \times 1$  mL). The combined EtOAc extracts were concentrated and the isolated product was

subjected to GC-MS analysis to determine the **3a:3b** selectivity (Table 1).

Representative procedure for the generalised Friedländer reaction (synthesis of ethyl 2-methyl-4-phenylquinoline-3carboxylate (Entry 1, Table 4): To the magnetically stirred mixture of 1 (0.49 g, 2.5 mmol) and 2 (0.33 g, 2.5 mmol, 0.32 mL) was added  $In(OTf)_3$  (0.07 g, 2.5 mmol, 5 mol%) and the reaction mixture was heated at 80 °C. After completion of the reaction (15 min, TLC), the reaction was cooled to rt and MeOH (5 mL) was added. The precipitated product was separated and recrystallized from hot MeOH to afford **3a** (0.67 g, 92 %) as yellow solid; identical (spectral data) with an authentic sample.<sup>3a</sup>

The remaining reactions were carried out following this general procedure. The purification was carried out by crystallization in hot methanol. In each occasion, the compounds were characterized (mp, IR, NMR, MS and HRMS). In general, the purification was made by crystallization. Wherever required, purification procedure was made by adsorbing the curde product on silica gel (2.5 g, 230-400 mesh size), charging on to a flash chromatography column of silica-gel (5 g, 230-400 mesh size), and eluting with hexane-EtOAc to obtain analytically pure compound (Table 4).

Methyl 2-methyl-4-phenylquinoline-3-carboxylate (Entry 2, Table 4)<sup>3g</sup>: Yellow solid; mp: 114-115 °C, (lit<sup>3g</sup> 107 °C); IR (KBr)  $v_{max}$ : 3055, 2951, 1730, 1582, 1225, 1173, 1064, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.08 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.45-7.47 (m, 4H), 7.36 (s, 2H), 7.26 (s, CHCl<sub>3</sub>), 3.57 (s, 3H), 2.77 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 169.0, 154.6, 147.8, 146.4, 135.7, 130.3, 129.2, 128.9, 128.5, 128.3, 127.3, 126.5, 126.4, 125.1, 76.7-77.3 (t, CHCl<sub>3</sub>), 52.2, 23.8; MS (APCl) *m/z* 278.16 (M+H)<sup>+</sup>.

*tert*-Butyl 2-methyl-4-phenylquinoline-3-carboxylate (Entry 3, Table 4)<sup>3g</sup>: Yellow solid; mp: 105-107 °C; (lit<sup>3g</sup> 107 °C); IR (KBr)  $v_{max}$ : 3412, 2972, 1580, 1566, 1370, 1242, 1165, 1058, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.06 (d, *J* = 8.4 Hz, 1H), 7.67-7.71 (m, 1H), 7.47-7.54 (m, 4H), 7.36-7.42 (m, 3H), 7.26 (s, CHCl<sub>3</sub>), 2.80 (s, 3H), 1.24 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 167.5, 154.5, 147.5, 145.4, 135.8, 130.0, 129.6, 128.8, 128.6, 128.3, 128.1, 126.4, 126.3, 125.4, 82.3, 76.7-77.3 (t, CHCl<sub>3</sub>), 27.6, 23.7; MS (APCI) *m/z* 319.96 (M+H)<sup>+</sup>.

Ethyl 7-chloro-2-methyl-4-phenylquinoline-3-carboxylate (Entry 4, Table 4)<sup>3g</sup>: Yellow solid; mp: 107-108 °C, (lit<sup>3g</sup> 104-105 °C); IR (KBr)  $v_{max}$ : 3056, 2935, 1715, 1565, 1340, 1295, 1030, 745, 660 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.02 (d, *J* = 6.5 Hz, 1H), 7.64-7.67 (m, 1H), 7.50-7.55 (m, 4H), 7.34-7.37 (m, 2H), 7.28 (s, CHCl<sub>3</sub>), 4.08 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 3H), 0.96 (t, *J* = 5.0 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm); 168.1, 155.0, 146.1, 145.4, 135.0, 132.4, 131.1, 130.5, 129.3, 128.8, 128.5, 128.2, 125.9, 125.2, 76.7-77.3 (t, CHCl<sub>3</sub>), 61.5, 23.8, 13.6; MS (APCI) *m/z* 326.45 (M+H)<sup>+</sup>.

Ethyl 2,4-dimethylquinoline-3-carboxylate (Entry 5, Table 4) <sup>4j</sup>: Yellow liquid; mp: 270-272 °C, (lit <sup>4j</sup> 271-272 °C); IR (KBr) v<sub>max</sub>: 2981, 1722, 1579, 1271, 1075, 1055, 852, 763 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.00 (t, *J* = 6.4 Hz, 2H), 7.72-7.68 (m, 1H), 7.55-7.51 (m, 1H), 7.27 (s, CHCl<sub>3</sub>), 4.48 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 2.65 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.2, 154.3, 147.1, 141.4, 130.0, 129.2, 127.9, 126.3, 125.7, 123.9, 76.7-77.3 (t, CHCl<sub>3</sub>), 61.7, 23.8, 15.7, 14.3; MS (APCI) *m/z* 230.11 (M+H)<sup>+</sup>.

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone (Entry 6, Table 4)<sup>3f</sup>: Brown solid; mp: 100-103 °C, (lit<sup>3f</sup> 111-112 °C); IR (KBr) v<sub>max</sub>: 3348, 3051, 1690, 1561, 1395, 1216, 1021, 714 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  (ppm) 8.08 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.0 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.51 (s, 3H), 7.44 (t, J = 7.6, 1H), 7.36 (d, J = 3.3, 2H), 7.26 (s, CHCl<sub>3</sub>), 2.70 (s, 3H), 2.00 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 205.7, 153.6, 147.5, 143.9, 135.2, 134.8, 130.1, 130.0, 128.9, 128.8, 128.7, 126.5, 126.1, 125.0, 76.7-77.3 (t, CHCl<sub>3</sub>), 31.9, 23.9; MS (APCI) *m/z* 262.18 (M+H)<sup>+</sup>.

6-chloro-2-methyl-4-phenylquinoline-3-carboxylate Methvl (Entry 7, Table 4)<sup>3f</sup>: Yellow solid; mp: 133-135 °C, (lit<sup>3f</sup> 133-135 °C); IR (KBr) v<sub>max</sub>: 3445, 3060, 2951, 2925, 2853, 1731, 1604, 1581, 1482, 1435, 1382, 1343, 1309, 1279, 1221, 1162, 1126, 1082, 1068, 950, 931 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.01 (d, J = 8.9 Hz, 1H), 7.65 (dd, J = 2.2 Hz, 1H), 7.49-7.55 (m, 4H), 7.34 (dd, J = 2.9 Hz, 2H), 7.26 (s, CHCl<sub>3</sub>), 3.58 (s, 3H), 2.75 (s, 3H);  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 168.6, 154.9, 146.1, 145.6, 134.9, 132.4, 131.3, 130.5, 129.1, 128.9, 128.5, 128.1, 125.9, 125.3, 76.7-77.3 (t, CHCl<sub>3</sub>), 52.3, 23.7; MS (APCI) *m/z* 312.76 (M+H)<sup>+</sup>.

#### (6-Chloro-2-methyl-4-phenylquinolin-3-

yl)(phenyl)methanone (Entry 8, Table 4)<sup>4k</sup>: Yellow solid; mp: 209-211 °C, (lit<sup>4k</sup> 209-211 °C); IR (KBr) v<sub>max</sub>: 3456, 3058, 2958, 2925, 2854, 1671, 1596, 1578, 1481, 1447, 1379, 1341, 1315, 1275, 1230, 1130, 1076, 1042, 1011, 968, 906, 879, 832, 786, 763, 723, 699, 601,513 cm  $^{\text{-1}};$   $^{1}\text{H}$  NMR (400 MHz, CDCl\_3):  $\delta$ (ppm) 8.09 (d, J = 8.9 Hz, 1H), 7.70 (dd, J = 2.2 Hz, 1H), 7.57-7.61 (m, 3H), 7.48 (t, J = 7.3 Hz, 1H), 7.28-7.33 (m, 5H), 7.28 (s, CHCl<sub>3</sub>), 7.20 (s, 2H), 2.63 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 197.4, 155.1, 146.2, 144.8, 136.9, 134.1, 133.7, 133.3, 132.5, 131.0, 130.6, 129.9, 129.2, 128.6, 128.5, 128.3, 126.2, 125.0, 76.7-77.3 (t, CHCl<sub>3</sub>), 24.0; MS (APCI) *m/z* 358.83 (M+H)<sup>+</sup>. 1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (Entry **9, Table 4)**<sup>3g</sup>: Yellow solid; mp: 149-152 °C, (lit<sup>3g</sup> 157 °C); IR (KBr) v<sub>max</sub>: 3460, 3051, 2926, 2855, 1918, 1702, 1567, 1479, 1354, 1196, 1126, 1079, 1048, 962, 936, 877, 857, 832, 790, 767, 710, 690, 642, 621, 582, 536, 477 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ ):  $\delta$  (ppm) 8.02 (d, J = 8.9 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.56 (d, J = 8.6 Hz, 4H), 7.35 (d, J = 3.4 Hz, 2H), 7.28 (s, CHCl<sub>3</sub>), 2.69 (s, 3H), 2.01 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCL<sub>3</sub>): δ (ppm) 205.3, 154.0, 145.9, 143.1, 135.5, 134.5, 132.5, 131.0, 130.5, 129.9, 129.3, 129.0, 125.9, 124.9, 76.7-77.3 (t, CHCl<sub>3</sub>), 31.9, 23.8; MS (APCI) m/z 296.76 (M+H)<sup>+</sup>.

(2-Methyl-4-phenylquinolin-3-yl)(phenyl)methanone (Entrv **10, Table 4)**<sup>4k</sup>: Yellow solid; mp: 132-135 °C, (lit<sup>4k</sup> 133-134 °C); IR (KBr)  $\nu_{max}$ : 3501, 3158, 2929, 2884, 1691, 1578, 1501, 1421, 1369, 1321, 1265, 1239, 1076, 1031, 945, 842, 783, 753, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.08 (d, J = 8.9 Hz, 1H), 7.68 (dd, J = 2.2 Hz, J = 9.2 Hz, 1H), 7.56-7.60 (m, 3H), 7.46 (t, J = 7.3 Hz, 1H), 7.26-7.32 (m, 5H), 7.19 (s, 3H), 2.62 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, CDCl\_3):  $\delta$  (ppm) 197.3, 155.0, 146.1, 144.7, 136.8, 134.0, 133.6, 133.2, 132.4, 131.0, 130.5, 129.9, 129.1,

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(APCI) *m/z* 324.38 (M+H)<sup>+</sup>. tert-Butyl 2,4-dimethylquinoline-3-carboxylate (Entry 11, Table 4): Yellow solid; mp: 109-110 °C; IR (KBr) v<sub>max</sub>: 3418, 2954, 1556, 1540, 1370, 1233, 1220, 1158, 1043, 761, 678 cm <sup>1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 7.82 (d, J = 7.8 Hz, 1H) 7.56 (d, J = 7.2 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 3.38 (s, 9H), 2.46 (s, 3H), 2.34 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm); 204.0, 160.0, 144.1, 138.5, 133.3, 131.6, 126.1, 126.0, 122.7, 119.6, 116.1, 81.3, 76.7-77.3 (t, CHCl<sub>3</sub>), 31.8, 22.4, 15.6; MS (APCI) *m/z* 258.31 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub>Na<sup>+</sup> [M+Na<sup>+</sup>], 280.1308; Found 280.1310.

128.5, 128.4, 128.3, 126.1, 124.9, 76.7-77.3 (t, CHCl<sub>3</sub>), 23.9; MS

9-Phenyl-3,4-dihydroacridin-1(2H)-one (Entry 12, Table 4)<sup>3g</sup>: Brown solid; mp: 156-158 °C, (lit  $^{3g}$  159 °C); IR (KBr)  $\nu_{max}$ : 3439, 3066, 2951, 2867, 1686, 1555, 1223, 1151, 755, 710 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.08 (d, J = 8.4 Hz, 1H), 7.76-7.80 (m, 1H), 7.39-7.43 (m, 1H), 7.47-7.54(m, 4H), 7.19-7.21 (m, 2H), 3.39 (t, J = 6.1 Hz, 2H), 2.72 (t, J = 6.8 Hz, 2H), 2.24-2.30 (m, 2H);  ${}^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm)  ${}^{13}$ C NMR (100 MHz, CDCl\_3):  $\delta$  (ppm) 198.1, 162.3, 151.5, 148.7, 137.7, 131.8, 128.5, 128.3, 128.1, 128.0, 127.6, 127.5, 126.4, 123.8, 76.7-77.3 (t, CHCl<sub>3</sub>), 40.7, 34.7, 21.4; MS (APCI) *m/z* 274.46 (M+H)<sup>+</sup>. 3-Methyl-9-phenyl-3,4-dihydroacridin-1(2H)-one (Entry 13, Table 4): Yellow solid; mp: 183-185 °C; IR (KBr) v<sub>max</sub>: 3425, 3051, 2955, 1690, 1555, 1211, 1040, 775, 703 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.06 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 6.7 Hz, 1H), 7.38-7.53 (m, 5H), 7.16-7.19 (m, 2H), 3.43-3.49 (m, 1H), 3.01-3.08 (m, 1H), 2.73-2.78 (m, 1H), 2.38-2.50 (m, 2H), 1.21 (d, J = 6.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 198.0, 161.7, 151.3, 148.8, 137.6, 131.8, 128.5, 128.3, 128.2, 128.1, 128.07, 128.01, 127.6, 127.5, 126.5, 123.2, 76.7-77.3 (t, CHCl<sub>3</sub>), 48.7, 42.9, 28.6, 21.3; MS (APCI) *m/z* 288.33 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for  $C_{20}H_{17}NONa^{+}$  [M+Na<sup>+</sup>], 310.1202; Found 310.1205.

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-1(2H)-one (Entry **14, Table 4)**<sup>4j</sup>: Yellow solid; mp: 239-241 °C, (lit<sup>4j</sup> 240-241 °C); IR (KBr) v<sub>max</sub>: 3352, 3065, 2931, 1943, 1688, 1552, 1372, 771, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.09 (d, J = 8.4 Hz, 1H), 7.62-7.80 (m, 1H), 7.49-7.54 (m, 4H), 7.40-7.44 (m, 1H), 7.19-7.21 (m, 2H), 3.29 (s, 2H), 2.59 (s, 2H), 1.18 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 198.0, 161.1, 151.0, 149.0, 137.6, 131.7, 128.5, 128.3, 128.1, 128.0, 127.6, 127.4, 126.5, 122.7, 76.7-77.3 (t, CHCl<sub>3</sub>), 54.2, 48.4, 32.3, 28.4; MS (APCI) *m/z* 302.29 (M+H)<sup>+</sup>.

3,9-Diphenyl-3,4-dihydroacridin-1(2H)-one (Entry 15, Table 4): Yellow solid; mp: 274 °C; IR (KBr)  $\nu_{max}\!:$  3432, 3025, 1691, 1551, 1488, 1381, 1215, 1048, 761  $\rm cm^{-1};\ ^1H\ NMR$  (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.11 (d, J = 8.4 Hz, 1H), 7.89-7.83 (m, 1H), 7.51-7.57 (m, 4H), 7.28-7.47 (m, 6H), 7.22-7.25 (m, 2H), 3.55-3.76 (m, 3H), 2.92-3.05 (m, 2H);  $^{13}$ C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 197.2, 161.2, 151.6, 149.0, 142.8, 137.5, 131.9, 129.0, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.1, 126.7, 126.6, 123.1, 76.7-77.3 (t, CHCl<sub>3</sub>), 47.8, 42.2, 39.0;; *m/z* 349.14 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for  $C_{25}H_{19}NONa^{+}$  [M+Na<sup>+</sup>], 372.1359; Found 372.1360.

9-Phenyl-2,3-Dihydro-1H-cyclopenta[b]quinoline (Entry 16, Table 4)<sup>4j</sup>: Yellow solid; mp: 129-131 °C, (lit<sup>4j</sup> 129-130 °C); IR (KBr)  $v_{max}$ : 3429, 3459, 2951, 1952, 1737, 1612, 1591, 1485, 1381, 1024, 762 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.08-8.10 (m, 1H), 7.61-7.66 (m, 2H), 7.46-7.66 (m, 3H), 7.37-7.40 (m, 3H), 7.28 (s, CHCl<sub>3</sub>), 3.23 (t, *J* = 7.7 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.14-2.21 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.4, 147.9, 142.7, 136.8, 133.6, 129.3, 128.8, 128.5, 128.2, 127.9, 126.2, 125.6, 125.5, 76.7-77.3 (t, CHCl<sub>3</sub>), 35.2, 30.3, 23.5; *m/z* 246.50 (M+H)<sup>+</sup>.

**9-Phenyl-1,2,3,4-tetrahydroacridine** (Entry 17, Table 4)<sup>38</sup>: Yellow solid; mp: 158-161 °C, (lit<sup>3g</sup> 131-132 °C); IR (KBr) v<sub>max</sub>: 3432, 3062, 2935, 1571, 1485, 1355, 1141 1072, 1024, 761, 705 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.04 (d, *J* = 8.4 Hz, 1H), 7.59-7.63 (m, 1H), 7.46-7.56 (m, 3H), 7.30-7.35 (m, 2H), 7.24-7.28 (m, 2H), 3.22 (t, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 6.5 Hz, 2H), 1.95-2.02 (m, 2H), 1.78-1.84 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 159.1, 146.5, 146.3, 137.2, 129.1, 128.6, 128.4, 128.3, 127.7, 126.7, 125.8, 125.4, 76.7-77.3 (t, CHCl<sub>3</sub>), 34.3, 28.1, 23.0, 22.9; MS (APCI) *m/z* 260.34 (M+H)<sup>+</sup>.

#### 11-Phenyl-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline

(Entry 18, Table 4): Yellow solid; mp: 110-111 °C; IR (KBr)  $v_{max}$ : 3442, 3051, 2925, 2851, 1607, 1572, 1481, 1191, 1021, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.03 (d, *J* = 8.3 Hz, 1H), 7.48-7.61 (m, 4H), 7.22-7.34 (m, 4H), 3.28 (d, *J* = 5.3 Hz, 2H), 2.70 (t, *J* = 5.03 Hz, 2H), 1.85 (s, 4H), 1.61 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 164.8, 145.8, 145.5, 137.7, 133.9, 129.5, 128.6, 128.4, 128.2, 127.6, 127.0, 126.4, 125.6, 76.7-77.3 (t, CHCl<sub>3</sub>), 40.2, 32.0, 30.7, 28.5, 27.1; MS (APCI) *m/z* 274.43 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for C<sub>20</sub>H<sub>19</sub>NNa<sup>+</sup> [M+Na<sup>+</sup>], 296.1410; Found 296.1407.

### 12-Phenyl-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline

**(Entry 19, Table 4)**<sup>4e</sup>: Yellow solid; mp: 214-215 °C; IR (KBr)  $v_{max}$ : 3061, 2961, 2925, 2855, 1552, 1571, 1445, 1272, 725, 706 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.05 (dd, *J* = 8.4 Hz and 0.4 Hz, 1H), 7.62-7.57 (m, 1H), 7.44-7.52 (m, 3H), 7.23-7.32 (m, 4H), 3.22-3.25 (m, 2H), 2.77 (t, *J* = 6.2 Hz, 2H), 1.91-2.04 (m, 2H), 1.35-1.53 (m, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 163.5, 146.5, 146.4, 137.6, 131.9, 129.6, 129.3, 128.5, 128.3, 128.2, 127.7, 127.3, 126.1, 125.4, 76.7-77.3 (t, CHCl<sub>3</sub>), 36.4, 31.3, 31.2, 28.1, 26.7, 25.8; MS (APCI) *m/z* 287.16 (M+H)<sup>+</sup>.

**2,4-Diphenylquinoline (Entry 20, Table 4):** Yellow solid; mp: 110-111 °C; IR (KBr)  $v_{max}$ : 3425, 3051, 2925, 1771, 1585, 1355, 1231, 1075, 1021, 766 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.17-8.20 (m, 3H), 7.91 (dd, *J* = 8.4 Hz and 0.8 Hz, 1H), 7.82 (s, 1H), 7.71-7.76 (m, 1H), 7.47-7.57 (m, 9H), 7.28 (s, CHCl<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 157.0, 149.1, 148.8, 139.7, 138.4, 130.1, 129.6, 129.5, 129.4, 128.9, 128.6, 128.4, 127.6, 126.3, 125.8, 125.7, 119.4, 76.7-77.3 (t, CHCl<sub>3</sub>); MS (APCl) *m/z* 282.40 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for C<sub>21</sub>H<sub>15</sub>NNa<sup>+</sup> [M+Na<sup>+</sup>], 304.1097; Found 304.1099.

**4-Phenyl-2-(thiophen-2-yl)quinoline (Entry 21, Table 4):** yellow solid; mp: 90-92 °C, (lit<sup>2b</sup> 89-92 °C); IR (KBr) v<sub>max</sub>: 3213, 2921, 1591, 1541, 1267, 812 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.18 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.32 Hz, 1H), 7.71-7.76 (m, 3H), 7.45-7.58 (m, 7H), 7.16-7.18 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 151.9, 149.0, 148.7, 145.4, 138.1, 129.7, 129.6, 129.5, 128.64, 128.60, 128.5, 128.1, 126.2, 125.93, 125.90, 125.7, 117.9, 76.7-77.3 (t, CHCl<sub>3</sub>); MS (APCl) m/z 288.10 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for C<sub>19</sub>H<sub>13</sub>NSNa<sup>+</sup>

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[M+Na<sup>+</sup>], 310.0661; Found 310.0663. **2-(Furan-2-yl)-4-phenylquinoline (Entry 22, Table 4)**: yellow solid; mp: 110-112 °C, (lit<sup>2b</sup> 109-111 °C); IR (neat) v<sub>max</sub>: 3051, 2834, 1589, 1540, 1256, 912 m<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.25 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.71-7.75 (m, 1H), 7.64 (d, *J* = 0.9 Hz, 1H), 7.52-7.57 (m, 5H), 7.45-7.49 (m, 1H), 7.31 (s, 1H), 6.61-6.62 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 153.7, 149.1, 148.7, 148.6, 141.1, 138.1, 129.74, 129.73, 129.5, 128.6, 128.5, 126.3, 125.8, 125.7, 117.7, 112.2, 110.2, 76.7-77.3 (t, CHCl<sub>3</sub>); MS (APCI) *m/z* 272.05 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for C<sub>19</sub>H<sub>13</sub>NONa<sup>+</sup> [M+Na<sup>+</sup>], 294.0889; Found 294.0887.

#### 2,2,2-Trifluoro-1-(2-methyl-4-phenylquinolin-3-yl)ethanone

**(Entry 23, Table 4):** Yellow solid; mp: 107-108 °C; IR (KBr)  $v_{max}$ : 3101, 2976, 2935, 1989, 1802, 1601, 1579, 1376, 1210, 1178, 1089, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.15 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 1.4 Hz, 1H), 7.70 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.50-7.54 (m, 4H) 7.35 (dd, *J* = 8.0, 2.1 Hz, 2H), 2.72 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm); 189.2, 153.4, 148.3, 147.6, 135.9, 133.7, 130.4, 129.9, 129.5, 128.7, 127.2, 126.3, 124.8, 124.5, 76.7-77.3 (t, CHCl<sub>3</sub>), 30.3, 23.8 ; MS (APCI) *m/z* 316.28 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for C<sub>18</sub>H<sub>12</sub>F<sub>3</sub>NONa<sup>+</sup> [M+Na<sup>+</sup>], 338.0763; Found 338.0765.

**2-Methyl-9-phenyl-1,2,3,4-tetrahydroacridine** (Entry 24, **Table 4):** Yellow solid; mp: 107-108 °C; IR (KBr)  $v_{max}$ : 3263, 2958, 1654, 1548, 1527, 1274, 809, 660 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.04 (d, *J* = 8.4 Hz, 1H), 7.59-7.63 (m, 1H), 7.47-7.57 (m, 3H), 7.32 (d, *J* = 3.7 Hz, 2H), 7.23-7.28 (m, 2H) 3.20-3.31 (m, 2H), 2.65-2.71 (m, 1H), 2.25 (q, *J* = 10.7 Hz, 1H), 2.04-2.09 (m, 1H), 1.60 (q, *J* = 5.64 Hz, 1H), 1.29 (d, *J* = 7.8 Hz, 1H), 1.02 (d, *J* = 6.56 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm); 158.8, 146.5, 146.3, 137.1, 129.2, 129.0, 128.7, 128.4, 128.3, 128.0, 126.6, 125.8, 125.4, 76.7-77.3 (t, CHCl<sub>3</sub>), 36.5, 33.9, 31.2, 29.3, 21.8; MS (APCI) *m/z* 274.37 (M+H)<sup>+</sup>. HRMS (ESI) m/z calcd for C<sub>20</sub>H<sub>19</sub>NNa<sup>+</sup> [M+Na<sup>+</sup>], 296.1410; Found 296.1412.

The influence of  $In(OTf)_3$  in the formation of 3a over 4 in performing the reaction of 1 with 2 in xylene.

Reaction of 1 with 2 in the absence of any catalyst in xylene. Representative procedure for the synthesis of 2-methyl-4phenylquinoline-3-carboxylic acid (4)

Following the literature procedure<sup>14</sup> 2-aminobenzophenone **1** (0.394 g, 2 mmol) and ethyl acetoacetate **2** (0.25 g, 2 mmol, 0.25 mL) in xylene (10 mL) was heated at 140 °C (oil bath) for 24 h. The mixture was cooled to rt, the residue was extracted with EtOAc ( $3 \times 1$  mL) and the combined EtOAc extracts were concentrated under reduced pressure. The crude product was adsorbed on silica gel (2 g, 60-120 mesh size), charged on to a column chromatography column of silica-gel (5 g, 60-120 mesh size), and eluted with hexane-EtOAc (90:10) to obtain analytically pure 2-methyl-4-phenylquinoline-3-carboxylic acid **4** (0.35 g, 68%) as light yellow solid; mp: 242-243 °C (lit<sup>14</sup> 243-244 °C); IR (KBr) v<sub>max</sub>: 3524, 3415, 3024, 2935, 1662, 1625, 1547, 1355 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.07 (d, J = 8.44 Hz, 1H), 7.71 (t, J = 7.48 Hz, 1H), 7.58 (d, J = 8.32 Hz, 1H), 7.46-7.51 (m, 3H), 7.42 (t, J = 7.56 Hz, 1H), 7.34-7.36 (m, 2H),

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2.78 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.0, 154.5, 147.8, 146.4, 135.7, 130.3, 129.4, 128.9, 128.5, 128.3, 127.3, 126.5, 126.4, 125.1, 76.7-77.3 (t, CHCl<sub>3</sub>), 23.8; MS (APCI) *m/z* 264.09 (M+H)<sup>+</sup>.

Reaction of 1 with 2 in the presence of  $In(OTf)_3$  as the catalyst in xylene. Representative procedure for the synthesis of 2methyl-4-phenylquinoline-3-carboxylate (3a). The mixture of 2-aminobenzophenone 1 (0.394 g, 2 mmol), ethyl acetoacetate 2 (0.25 g, 2 mmol, 0.25 mL), and  $In(OTf)_3$  (0.05 g, 2.0 mmol, 5 mol%) in xylene (10 mL) was heated at 140 °C (oil bath) for 24 h. The mixture was cooled to rt, the residue was extracted with EtOAc (3 × 1 mL) and the combined EtOAc extracts were concentrated under reduced pressure. The crude product was adsorbed on silica gel (2 g, 60-120 mesh size), charged on to a column chromatography column of silica-gel (5 g, 60-120 mesh size), and eluted with hexane-EtOAc (90:10) to afford 2methyl-4-phenylquinoline-3-carboxylate **3a** (0.25 g, 45%) as light yellow solid; identical (spectral data) with an authentic sample.<sup>3a</sup>

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# Friedländer annulation: Scope and limitations of metal Lewis acid catalysts in selectivity control for the synthesis of functionalised quinolines

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 $In(OTf)_3$  is the most effective catalyst from metal halides, tetrafluoroborates, perchlorates, and triflates for Friedländer quinoline synthesis in 75-92% yields.