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ARTICLE

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

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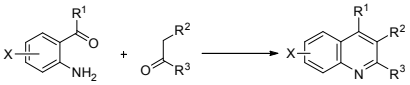
The scope and limitations of metal salt Lewis acid catalysts were examined for the selectivity control for the formation of Friedländer and non-Friedländer product during the reaction involving 2-aminobenzophenone and ethyl acetoacetate. From a pool of metal halides, tetrafluoroborates, perchlorates, 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., β-ketoesters, cyclic/acyclic β-diketones, cyclic/acylic ketones, and aryl/heteroaryl methyl ketones) under solvent-free conditions affording the desired quinolines in 75-92% yields.

Introduction

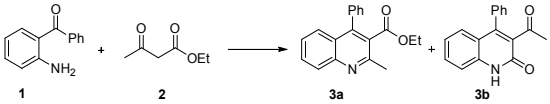
The broad spectrum of biological activities of quinolines in diverse therapeutic areas[1] has generated perpetual interest to develop newer synthetic methods for the preparation of this privileged class of compounds.

Friedländer annulation, the acid or base-catalysed cyclo-condensation of 2-amino-substituted aromatic aldehydes/ketones with carbonyl derivatives containing active-methylene 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.[2] Different Brønsted[3] and Lewis[4] acids have been used as catalysts offering advantages over the thermal processes[5] or the base-catalysed reactions.[6] However, in some of these methodologies the ketones (e.g., 2-aminobenzophenone) fail to react with ethyl acetoacetate to afford the desired quinoline.[7]



Scheme 1. Friedländer annulation reaction.

The selectivity control[8] often becomes a bottleneck in organic synthesis. Such a situation is envisaged during the cyclocondensation of 2-aminoaryl ketones with β-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[9] followed by intramolecular Knoevenagel condensation of the aryl ketone with the active methylene group of the intermediate Schiff base,[10] (ii) Knoevenagel condensation of the aryl ketone with the active methylene group of the reacting partner followed by intramolecular imine formation[11] (Scheme 3). The un-catalysed process may lead to the formation of the non-Friedländer product[7,12] via initial amide formation by the reaction of the amino group with the ester carbonyl of ethyl acetoacetate

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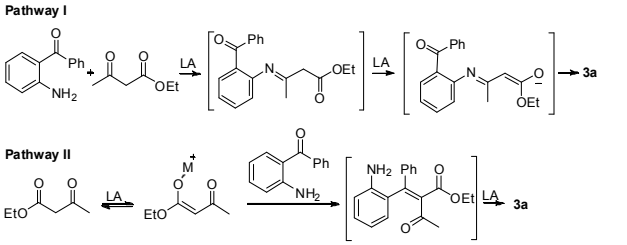
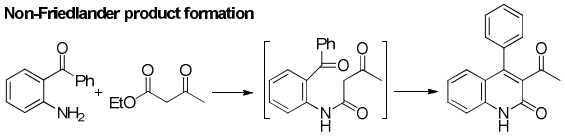
followed by intramolecular Knoevenagel condensation (Scheme 4). The use of base catalysts also direct the reaction towards the formation of the non-Friedländer product.[7,13] The recent report[14] on Friedländer reaction without using any catalyst, however, is associated with the hydrolytic decomposition 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 quinolines.



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.

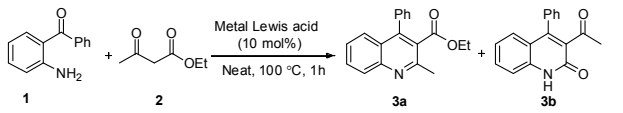
As metal salt of a strong protic acid should be a strong Lewis acid, metal triflates could be ideal catalyst as TfOH is the strongest protic acid (H_0 = −14.1).[15] However, the possibility of ligand exchange of metal triflates during the progress of the reaction often raises query as to the nature of the actual catalytic species/agent. Although $HNTf_2$ is a weaker Brønsted acid than TfOH[16] and ligand exchange is usually not observed with metal triflimides,[17] the high cost and lack of commercially availability make metal triflimides less popular. Although a few metal triflates have been used for quinoline synthesis via Friedländer annulation[4h-j] the issue of selectivity control for the Friedländer versus non-Friedländer product formation remained unaddressed and in some cases[4i] 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 solvent-free 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 $Zn(OTf)_2$, $In(OTf)_3$, $Gd(OTf)_3$, $Dy(OTf)_3$, and $Al(OTf)_3$ 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 $In(OTf)_3$ > $Zn(OTf)_2$ ~ $Gd(OTf)_3$ ~ $Dy(OTf)_3$ ~ $Al(OTf)_3$ ~ $Er(OTf)_3$ > $Sc(OTf)_3$ ~ $Sm(OTf)_2$ > $Mg(OTf)_2$ ~ $Cu(OTf)_2$ ~ $Nd(OTf)_3$ ~ $La(OTf)_3$ ~ $Ho(OTf)_3$ > AgOTf.

As the metal perchlorates[9a,b,18] appear to be the next best effective electrophilic activating agents it was next planned to investigate the use of metal perchlorates.[19] Among Zn, Fe, Cu, Zr, In, Bi, Al, Mg, and Li-perchlorates the use of $Zn(ClO_4)_2{\cdot}xH_2O$ 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 $LiClO_4$, 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 $Zn(ClO_4)_2{\cdot}xH_2O$ > $Mg(ClO_4)_2{\cdot}6H_2O$ > $Cu(ClO_4)_2{\cdot}6H_2O$ > $In(ClO_4)_3{\cdot}6H_2O$ > $ZrO(ClO_4)_2{\cdot}xH_2O$ > $BiOClO_4{\cdot}xH_2O$ ~ $Fe(ClO_4)_3{\cdot}xH_2O$ > $Al(ClO_4)_3{\cdot}9H_2O$ > $LiClO_4$.

Metal tetrafluoroborates, derived from weaker Brønsted acid such as HBF_4, are expected to be milder Lewis acid catalysts and are known to catalyze various organic reactions.[20] 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 $Zn(BF_4)_2$ 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 $Zn(BF_4)_2$ > $AgBF_4$ ~ $Cu(BF_4)_2$ > $Co(BF_4)_2$ > $Fe(BF_4)_2{\cdot}xH_2O$.

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 $HfCl_4$ affording **3a** in 84% yield with 100% selectivity. However, the use of $CeCl_3{\cdot}7H_2O$ 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]



Entry	Catalyst	Yield (%)[b] (3a + 3b)	Selectivity[c] 3a	3b
1	None	45	traces	100
		Metal triflates		
2	$Zn(OTf)_2$	81	100	00
3	$Mg(OTf)_2$	80	90	10
4	$Er(OTf)_3$	82	98	00
5	$In(OTf)_3$	90	100	00
6	$Cu(OTf)_2$	75	90	10
7	$Sc(OTf)_3$	83	94	06
8	$Gd(OTf)_3$	85	100	00
9	$Sm(OTf)_2$	81	94	06
10	$Dy(OTf)_3$	84	100	00
11	$Nd(OTf)_3$	80	90	10
12	$Al(OTf)_3$	81	100	00
13	AgOTf	72	70	30
14	$La(OTf)_3$	77	90	10
15	$Ho(OTf)_3$	85	90	10
		Metal perchlorates		

16	$Zn(ClO_4)_2·xH_2O$	82	100	00
17	$Fe(ClO_4)_3·xH_2O$	72	70	30
18	$Cu(ClO_4)_2·6H_2O$	81	90	10
19	$ZrO(ClO_4)_2·xH_2O$	70	75	25
20	$In(ClO_4)_3·6H_2O$	76	85	15
21	$BiOClO_4·xH_2O$	65	75	25
22	$Al(ClO_4)_3·9H_2O$	65	60	40
23	$Mg(ClO_4)_2·6H_2O$	82	95	05
24	$LiClO_4$	62	40	60
	Metal tetrafluoroborates			
25	$Zn(BF_4)_2$	91	100	00
26	$Fe(BF_4)_2·xH_2O$	84	70	30
27	$AgBF_4$	72	85	15
28	$Cu(BF_4)_2$	78	85	15
29	$Co(BF_4)_2$	69	75	25
	Metal halides			
30	InF_3	72	90	10
31	$InCl_3$	78	98	00
32	$InBr_3$	70	85	15
33	InI_3	72	82	18
34	$ZrCl_4$	69	85	15
35	$GaCl_3$	70	84	16
36	$NbCl_5$	63	70	30
37	$HfCl_4$	84	100	00

[a]**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. [b]Isolated yield of the products (**3a** and **3b**). [c]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 [$Zn(BF_4)_2$, $Zn(ClO_4)_2·xH_2O$, $Mg(ClO_4)_2·6H_2O$, $Zn(OTf)_2$, $Mg(OTf)_2$, $Er(OTf)_3$, $In(OTf)_3$, $Cu(OTf)_2$, $Sm(OTf)_2$, $Gd(OTf)_3$, $Sc(OTf)_3$, $Gd(OTf)_3$, $Nd(OTf)_3$, $Al(OTf)_3$, $Dy(OTf)_3$, $HfCl_4$] 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 $Er(OTf)_3$, $In(OTf)_3$ and $Sc(OTf)_3$ 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 $Er(OTf)_3$ and $Sc(OTf)_3$.†

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]

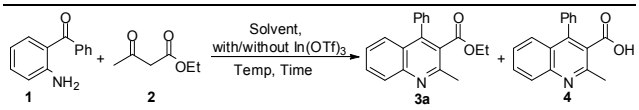
Entry	Catalyst	Time (min)	Temp (°C)	Yield (%)[b]
1	$Zn(BF_4)_2$	60	100	100
2		30	100	62
3		15	100	39
4	$Zn(ClO_4)_2·xH_2O$	60	100	100
5		30	100	73
6		15	100	55
7	$Mg(ClO_4)_2·6H_2O$	60	100	96
8		30	100	62
9		15	100	55
10	$Zn(OTf)_2$	60	100	100
11		30	100	72
12		15	100	61
13	$Mg(OTf)_2$	60	100	94
14		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	$Cu(OTf)_2$	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	$Nd(OTf)_3$	60	100	92
38		30	100	65
39		15	100	43
40	$Al(OTf)_3$	60	100	98
41		30	100	61
42		15	100	41
43	$HfCl_4$	60	100	99
44		30	100	56
45		15	100	31
46	$InCl_3$	60	100	98
47		30	100	64
48		15	100	46
49	$In(OTf)_3$	10	100	72
50	$Sc(OTf)_3$	10	100	75
51	$Er(OTf)_3$	10	100	70
52	$In(OTf)_3$	30	80	100
53	$Sc(OTf)_3$	30	80	98
54	$Er(OTf)_3$	30	80	95
55	$In(OTf)_3$	10	80	70
56	$Sc(OTf)_3$	10	80	68
57	$Er(OTf)_3$	10	80	67
58	$In(OTf)_3$	15	80	100
59	$Sc(OTf)_3$	15	80	96
60	$Er(OTf)_3$	15	80	95
61	$In(OTf)_3$	30	60	50
62	$Sc(OTf)_3$	30	60	45
63	$Er(OTf)_3$	30	60	40
64	$In(OTf)_3$	15	50	35
65	$Sc(OTf)_3$	15	50	32
66	$Er(OTf)_3$	15	50	32
67	$In(OTf)_3$	15	80	98[c]
68	$Sc(OTf)_3$	15	80	95[c]
69	$Er(OTf)_3$	15	80	98[c]

[a]**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. [b]Yield of **3a** (GC-MS). [c]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 $In(OTf)_3$ 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

time. The use of non-polar solvent such as PhMe afforded poor result (entry 6). However, contrary to the recent report[14] on catalyst-free quinoline synthesis that led to the formation of the corresponding carboxylic acid due to hydrolytic decomposition of the final product, the $In(OTf)_3$ 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 $In(OTf)_3$ 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[14] 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 $In(OTf)_3$ (5 mol%) the desired ester **3a** was formed (entries 6-9 and 14-20, table 3). These results clearly demonstrate that the use of $In(OTf)_3$ 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 $In(OTf)_3$-catalysed Friedländer annulation to form **3a**/**4**.[a]

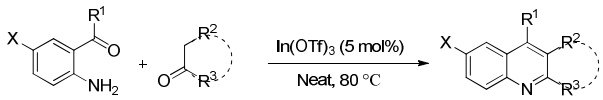


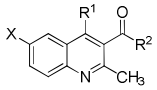
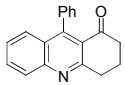
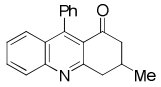
Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	
				3a	**4**
1	Neat	80	15 min	100	00
2	Neat	rt	2	65	00
3	EtOH	80	15 min	82	00
4	EtOH	80	45 min	96	00
5	EtOH	rt	2	85	00
6	DMSO	80	15 min	46	00
7	DMF	80	15 min	65	00
8	THF	80	15 min	64	00
9	PhMe	80	15 min	32	00
10	PhMe	80	1	43	00
11	PhMe	110	15 min	35	00
12	PhMe	110	1	48	00
13	PhMe[c]	80	1	00	00
14	PhMe[c]	80	24	00	43 (40)[d]
15	PhMe[c]	110	1	00	00
16	PhMe[c]	110	24	00	65 (62)[d]
17	Xylene	80	15 min	40	00
18	Xylene	80	1	28	00
19	Xylene	80	24	42	00
20	Xylene	110	1	34	00
21	Xylene	110	24	46	00
22	Xylene	140	1	38	00
23	Xylene	140	24	49 (45)[e]	00
24	Xylene[c]	80	1	00	00
25	Xylene[c]	80	24	00	37 (30)[d]
26	Xylene[c]	110	1	00	00
27	Xylene[c]	110	24	00	42 (40)[d]
28	Xylene[c]	140	1	00	00
29	Xylene[c]	140	24	00	71 (68)[d]
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

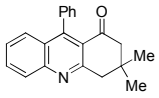
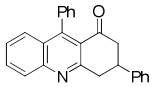
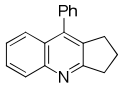
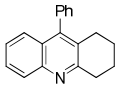
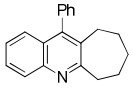
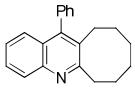
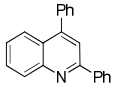
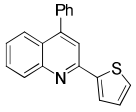
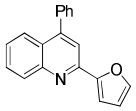
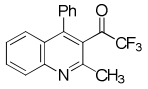
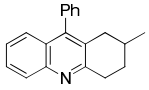
[a] **1** (0.197 g, 1 mmol) was treated with **2** (0.13 g, 1 mmol, 1 equiv) in the presence of $In(OTf)_3$ (5 mol%) (except for entries 10-13, and 21-26) in different solvent (5 mL) at the indicated temperature (oil bath) for the stipulated time. [b] The GC-MS yield of **3a** and **4** unless otherwise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

The catalytic potential of $In(OTf)_3$ 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 β-ketoesters such as methyl acetoacetate, ethyl acetoacetate and ^{t}-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, table 4), 2-acetylthiophene (entry 21, table 4), and 2-acetylfuran (entry 22, table 4).

Table 4. $In(OTf)_3$-Catalysed Friedländer annulations to synthesise functionalized quinolines.[a]



Entry	Product	Time (min)	Yield (%)[b]
			
1	X = H; R^1 = Ph; R^2 = OEt	15	92
2	X = H; R^1 = Ph; R^2 = OMe	15	90
3	X = H; R^1 = Ph; R^2 = O^{t}Bu	15	88
4	X = Cl; R^1 = Ph; R^2 = OEt	20	82
5	X = H; R^1 = Me; R^2 = OEt	30	85
6	X = H; R^1 = Ph; R^2 = Me	20	83
7	X = Cl; R^1 = Ph; R^2 = OMe	15	87
8	X = Cl; R^1 = Ph; R^2 = Ph	20	81
9	X = Cl; R^1 = Ph; R^2 = Me	15	84
10	X = H; R^1 = Ph; R^2 = Ph	20	80
11	X = H; R^1 = Me; R^2 = O^{t}Bu	20	78
12		25	82
13		30	81

14		30	85
15		30	78
16		20	83
17		20	85
18		20	80
19		20	76
20		40	76
21		40	76
22		45	75
23		40	72
24		45	81

[a]2-Aminoketone (2.5 mmol) was treated with β-ketoester/β-diketone or ketone (2.5 mmol, 1 equiv) in the presence of $In(OTf)_3$ (5 mol%) under neat conditions at 80 °C for stipulated time. [b]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 $In(OTf)_3$ with the reported catalysts during the reaction of **1** with **2** for the formation of **3a**.[a]

Entry	Catalyst	Yield (%)[b,c]	Lit. Ref.
1	Sulfamic acid	79	3a
2	$SnCl_2$•$2H_2O$	00	4e
3	$Nd(NO_3)_3$•$6H_2O$	00	4d
4	*p*-TsOH	43 (11)	10a
5	I_2	00	4f
6	Oxalic acid	41 (15)	3d
7	TFA	72	3e
8	CAN	00	4g
9	$Yb(OTf)_3$	66 (10)	4j
10	$Cu(OTf)_2$	61	4h
11	$In(OTf)_3$	90	present work

[a]**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. [b]Isolated yield of the Friendlander product **3a**. [c]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 β-ketoesters, cyclic/acyclic β-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 ^1H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3/CD_3OD/(CD_3)_2SO$ with residual undeuterated solvent ($CHCl_3$: 7.26/77.0)/(CH_3OH: 3.31/49.0)/[$(CH_3)_2SO$: 2.50/39.52] using Me_4Si as an internal standard. The chemical shift (δ) values are given in ppm and *J* values are given in Hz. The ^{13}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^{-1} as KBr pellets for all solid samples.

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).[3a]

The authentic sample of **3a** was prepared with minor modification of reported literature method. The mixture of 2-aminobenzophenone **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 ^{o}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 × 1 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-4-phenylquinoline-3-carboxylate (**3a**) (0.23 g, 81 %) as yellow solid; mp: 98-100 °C (lit[3a] 97 °C); IR (KBr) ν_{max}: 3054, 2976, 1715, 1402, 1236, 1077 cm-^{1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (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); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 61.3, 23.8, 13.6; MS (APCI) *m/z* 292.23 $(M+H)^+$.

Synthesis of authentic sample of 3-acetyl-4-phenylquinolin-2(1*H*)-one (3b).[12]

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 3-acetyl-4-phenylquinolin-2(1*H*)-one (**3b**) (400 mg, 61%) as off-white needles; mp: 255-258 °C, (lit[12] 256-258 °C); IR (KBr) ν_{max}: 3105, 2988, 1830, 1642, 1325, 1281, 1188, 805 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): 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); ^{13}C NMR (100 MHz, CD_3OD): 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 $(M+H)^+$.

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 × 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-3-carboxylate (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.[3a]

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)[3g]: Yellow solid; mp: 114-115 °C, (lit[3g] 107 °C); IR (KBr) ν_{max}: 3055, 2951, 1730, 1582, 1225, 1173, 1064, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CHCl_3$), 3.57 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 52.2, 23.8; MS (APCI) *m/z* 278.16 $(M+H)^+$.

***tert*-Butyl 2-methyl-4-phenylquinoline-3-carboxylate (Entry 3, Table 4)[3g]:** Yellow solid; mp: 105-107 °C; (lit[3g] 107 °C); IR (KBr) ν_{max}: 3412, 2972, 1580, 1566, 1370, 1242, 1165, 1058, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CHCl_3$), 2.80 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 27.6, 23.7; MS (APCI) *m/z* 319.96 $(M+H)^+$.

Ethyl 7-chloro-2-methyl-4-phenylquinoline-3-carboxylate (Entry 4, Table 4)[3g]: Yellow solid; mp: 107-108 °C, (lit[3g] 104-105 °C); IR (KBr) ν_{max}: 3056, 2935, 1715, 1565, 1340, 1295, 1030, 745, 660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 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, $CHCl_3$), 4.08 (q, *J* = 7.1 Hz, 2H), 2.78 (s, 3H), 0.96 (t, *J* = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 61.5, 23.8, 13.6; MS (APCI) *m/z* 326.45 $(M+H)^+$.

Ethyl 2,4-dimethylquinoline-3-carboxylate (Entry 5, Table 4) [4j]: Yellow liquid; mp: 270-272 °C, (lit[4j] 271-272 °C); IR (KBr) ν_{max}: 2981, 1722, 1579, 1271, 1075, 1055, 852, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.00 (t, *J* = 6.4 Hz, 2H), 7.72-7.68 (m, 1H), 7.55-7.51 (m, 1H), 7.27 (s, $CHCl_3$), 4.48 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 2.65 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$): δ (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, $CHCl_3$), 61.7, 23.8, 15.7, 14.3; MS (APCI) *m/z* 230.11 $(M+H)^+$.

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone (Entry 6, Table 4)[3f]: Brown solid; mp: 100-103 °C, (lit[3f] 111-112 °C); IR (KBr) ν_{max}: 3348, 3051, 1690, 1561, 1395, 1216, 1021, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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, $CHCl_3$), 2.70 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 31.9, 23.9; MS (APCI) *m/z* 262.18 $(M+H)^+$.

Methyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (Entry 7, Table 4)[3f]: Yellow solid; mp: 133-135 °C, (lit[3f] 133-135 °C); IR (KBr) ν_{max}: 3445, 3060, 2951, 2925, 2853, 1731, 1604, 1581, 1482, 1435, 1382, 1343, 1309, 1279, 1221, 1162, 1126, 1082, 1068, 950, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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, $CHCl_3$), 3.58 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 52.3, 23.7; MS (APCI) *m/z* 312.76 $(M+H)^+$.

(6-Chloro-2-methyl-4-phenylquinolin-3-yl)(phenyl)methanone (Entry 8, Table 4)[4k]: Yellow solid; mp: 209-211 °C, (lit[4k] 209-211 °C); IR (KBr) ν_{max}: 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^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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, $CHCl_3$), 7.20 (s, 2H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 24.0; MS (APCI) *m/z* 358.83 $(M+H)^+$.

1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (Entry 9, Table 4)[3g]: Yellow solid; mp: 149-152 °C, (lit[3g] 157 °C); IR (KBr) ν_{max}: 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^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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, $CHCl_3$), 2.69 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCL_3$): 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, $CHCl_3$), 31.9, 23.8; MS (APCI) *m/z* 296.76 $(M+H)^+$.

(2-Methyl-4-phenylquinolin-3-yl)(phenyl)methanone (Entry 10, Table 4)[4k]: Yellow solid; mp: 132-135 °C, (lit[4k] 133-134 °C); IR (KBr) ν_{max}: 3501, 3158, 2929, 2884, 1691, 1578, 1501, 1421, 1369, 1321, 1265, 1239, 1076, 1031, 945, 842, 783, 753, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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}C NMR (100 MHz, $CDCl_3$): δ (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, 128.5, 128.4, 128.3, 126.1, 124.9, 76.7-77.3 (t, $CHCl_3$), 23.9; MS (APCI) *m/z* 324.38 $(M+H)^+$.

***tert*-Butyl 2,4-dimethylquinoline-3-carboxylate (Entry 11, Table 4):** Yellow solid; mp: 109-110 °C; IR (KBr) ν_{max}: 3418, 2954, 1556, 1540, 1370, 1233, 1220, 1158, 1043, 761, 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 31.8, 22.4, 15.6; MS (APCI) *m/z* 258.31 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{16}H_{19}NO_2Na^+$ $[M+Na^+]$, 280.1308; Found 280.1310.

9-Phenyl-3,4-dihydroacridin-1(2*H*)-one (Entry 12, Table 4)[3g]: Brown solid; mp: 156-158 °C, (lit[3g] 159 °C); IR (KBr) ν_{max}: 3439, 3066, 2951, 2867, 1686, 1555, 1223, 1151, 755, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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, $CDCl_3$): δ (ppm) ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 40.7, 34.7, 21.4; MS (APCI) *m/z* 274.46 $(M+H)^+$.

3-Methyl-9-phenyl-3,4-dihydroacridin-1(2*H*)-one (Entry 13, Table 4): Yellow solid; mp: 183-185 °C; IR (KBr) ν_{max}: 3425, 3051, 2955, 1690, 1555, 1211, 1040, 775, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 48.7, 42.9, 28.6, 21.3; MS (APCI) *m/z* 288.33 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{20}H_{17}NONa^+$ $[M+Na^+]$, 310.1202; Found 310.1205.

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-1(2*H*)-one (Entry 14, Table 4)[4j]: Yellow solid; mp: 239-241 °C, (lit[4j] 240-241 °C); IR (KBr) ν_{max}: 3352, 3065, 2931, 1943, 1688, 1552, 1372, 771, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 54.2, 48.4, 32.3, 28.4; MS (APCI) *m/z* 302.29 $(M+H)^+$.

3,9-Diphenyl-3,4-dihydroacridin-1(2*H*)-one (Entry 15, Table 4): Yellow solid; mp: 274 °C; IR (KBr) ν_{max}: 3432, 3025, 1691, 1551, 1488, 1381, 1215, 1048, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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, $CDCl_3$): δ (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, $CHCl_3$), 47.8, 42.2, 39.0;; *m/z* 349.14 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{25}H_{19}NONa^+$ $[M+Na^+]$, 372.1359; Found 372.1360.

9-Phenyl-2,3-Dihydro-1*H*-cyclopenta[b]quinoline (Entry 16, Table 4)[4j]: Yellow solid; mp: 129-131 °C, (lit[4j] 129-130 °C); IR

(KBr) ν_{max}: 3429, 3459, 2951, 1952, 1737, 1612, 1591, 1485, 1381, 1024, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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, $CHCl_3$), 3.23 (t, *J* = 7.7 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.14-2.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 35.2, 30.3, 23.5; *m/z* 246.50 $(M+H)^+$.

9-Phenyl-1,2,3,4-tetrahydroacridine (Entry 17, Table 4)[3g]: Yellow solid; mp: 158-161 °C, (lit[3g] 131-132 °C); IR (KBr) ν_{max}: 3432, 3062, 2935, 1571, 1485, 1355, 1141 1072, 1024, 761, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 34.3, 28.1, 23.0, 22.9; MS (APCI) *m/z* 260.34 $(M+H)^+$.

11-Phenyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[b]quinoline (Entry 18, Table 4): Yellow solid; mp: 110-111 °C; IR (KBr) ν_{max}: 3442, 3051, 2925, 2851, 1607, 1572, 1481, 1191, 1021, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 40.2, 32.0, 30.7, 28.5, 27.1; MS (APCI) *m/z* 274.43 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{20}H_{19}NNa^+$ $[M+Na^+]$, 296.1410; Found 296.1407.

12-Phenyl-6,7,8,9,10,11-hexahydrocycloocta[b]quinoline (Entry 19, Table 4)[4e]: Yellow solid; mp: 214-215 °C; IR (KBr) ν_{max}: 3061, 2961, 2925, 2855, 1552, 1571, 1445, 1272, 725, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$), 36.4, 31.3, 31.2, 28.1, 26.7, 25.8; MS (APCI) *m/z* 287.16 $(M+H)^+$.

2,4-Diphenylquinoline (Entry 20, Table 4): Yellow solid; mp: 110-111 °C; IR (KBr) ν_{max}: 3425, 3051, 2925, 1771, 1585, 1355, 1231, 1075, 1021, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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, $CHCl_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$); MS (APCI) *m/z* 282.40 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{21}H_{15}NNa^+$ $[M+Na^+]$, 304.1097; Found 304.1099.

4-Phenyl-2-(thiophen-2-yl)quinoline (Entry 21, Table 4): yellow solid**;** mp: 90-92 °C, (lit[2b] 89-92 °C); IR (KBr) ν_{max}: 3213, 2921, 1591, 1541, 1267, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$); MS (APCI) *m/z* 288.10 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{19}H_{13}NSNa^+$ $[M+Na^+]$, 310.0661; Found 310.0663.

2-(Furan-2-yl)-4-phenylquinoline (Entry 22, Table 4): yellow solid; mp: 110-112 °C, (lit[2b] 109-111 °C); IR (neat) ν_{max}: 3051, 2834, 1589, 1540, 1256, 912 m^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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, $CHCl_3$); MS (APCI) *m/z* 272.05 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{19}H_{13}NONa^+$ $[M+Na^+]$, 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) ν_{max}: 3101, 2976, 2935, 1989, 1802, 1601, 1579, 1376, 1210, 1178, 1089, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 30.3, 23.8 ; MS (APCI) *m/z* 316.28 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{18}H_{12}F_3NONa^+$ $[M+Na^+]$, 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) ν_{max}: 3263, 2958, 1654, 1548, 1527, 1274, 809, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 36.5, 33.9, 31.2, 29.3, 21.8; MS (APCI) *m/z* 274.37 $(M+H)^+$. HRMS (ESI) m/z calcd for $C_{20}H_{19}NNa^+$ $[M+Na^+]$, 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-4-phenylquinoline-3-carboxylic acid (4)

Following the literature procedure[14] 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 × 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[14] 243-244 °C); IR (KBr) ν_{max}: 3524, 3415, 3024, 2935, 1662, 1625, 1547, 1355 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (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),

2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (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, $CHCl_3$), 23.8; MS (APCI) *m/z* 264.09 $(M+H)^+$.

Reaction of 1 with 2 in the presence of In(OTf)$_3$ as the catalyst in xylene. Representative procedure for the synthesis of 2-methyl-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 ^oC (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 2-methyl-4-phenylquinoline-3-carboxylate **3a** (0.25 g, 45%) as light yellow solid; identical (spectral data) with an authentic sample.[3a]

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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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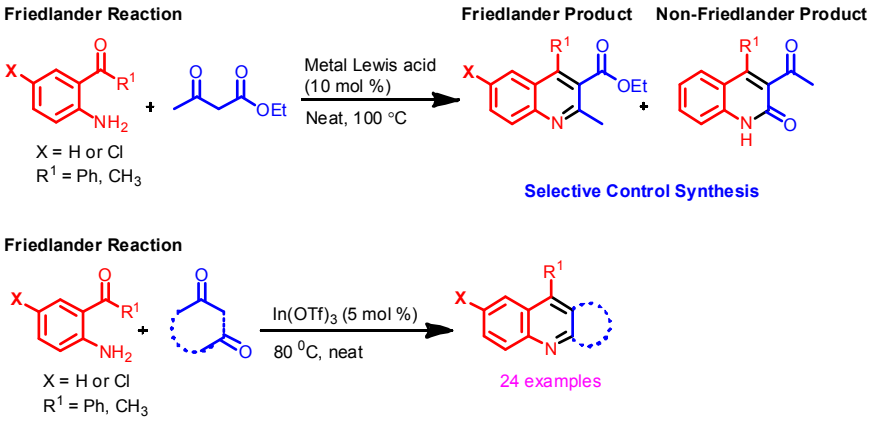

$In(OTf)_3$ is the most effective catalyst from metal halides, tetrafluoroborates, perchlorates, and triflates for Friedländer quinoline synthesis in 75-92% yields.