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$InCl_3$-Driven Regioselective Synthesis of Functionalized/Annulated Quinolines: Scope and Limitations

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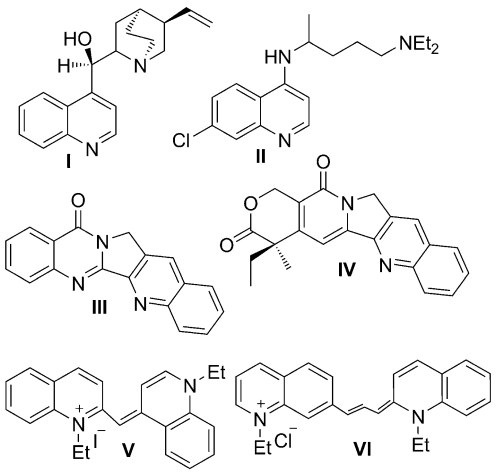
Abstract: The efficient, regioselective synthesis of functionalized/annulated quinolines was achieved by the coupling of 2-aminoaryl ketones with alkynes/active methylenes/α-oxoketene dithioacetals promoted by $InCl_3$ in refluxing acetonitrile as well as under solvent-free conditions in excellent yields. This transformation presumably proceeded through the hydroamination–hydroarylation of alkynes, and the Friedländer annulation of active methylene compounds and α-oxoketene dithioacetals with 2-aminoarylketones. In addition, simple reductive and oxidative cyclization of 2-nitrobenzaldehyde and 2-aminobenzylalcohol, respectively, afforded substituted quinolines. Systematic optimization of the reaction parameters allowed us to identify two-component coupling (2CC) conditions that were tolerant of a wide range of functional groups, thereby providing densely functionalized/annulated quinolines. This approach tolerates the synthesis of various bioactive quinoline frameworks from the same 2-aminoarylketones under mild conditions, thus making this strategy highly useful in diversity-oriented synthesis (DOS). The scope and limitations of the alkyne-, activated methylene-, and α-oxoketene dithioacetal components on the reaction were also investigated.

Keywords: annulation · cyclization · indium · quinolines · solvent-free synthesis

Introduction

Quinolines are an important class of heterocyclic alkaloids that are important synthetic targets for the pharmaceutical industry as well as in academic laboratories because of their rich chemistry and numerous applications. They are widely present as key structural motifs in many natural products and in a large number of bioactive drugs, such as quinine[1] (**I**), chloroquine[2] (**II**), luotonine A[3] (**III**), and camptothecin[4] (**IV**; Scheme 1). Numerous quinoline derivatives have been developed that have useful biological activity, such as anti-malarial,[5] anti-bacterial,[6] anti-inflammatory,[7] anti-cancer,[8] anti-diabetic,[9] anti-asthmatic,[10] anti-hypertensive,[11] anti-alzheimer,[12] and anti-platelet activity,[13] HIV-1 replication inhibitor,[14] CysLT (LTD_4) receptor antagonist,[15] and tyrosine kinase inhibitor.[16] In addition, sulfur-containing fused-thienoquinolines exhibit a number of pharmacological activities.[17] Furthermore, many quinoline derivatives have been utilized as chemo- and fluorescent-sensors for fluoride ions[18] and other metal ions in aqueous solution.[19] In particular, some quinolines are valuable synthons for the preparation of nano- and *meso*-structures with enhanced electronic as well as photonic functions,[20] and are well-known ligands for the preparation of phosphorescent complexes for organic light emitting diodes (OLEDs).[21] At the dawn of the nineteenth century, some quinoline dyes, such as ethyl red (**V**) and pinacyanol (**VI**; Scheme 1), were used in the first photographic plate.[22] Because of their importance as substructures in a broad range of natural and synthetic products, significant efforts have been made to construct new quinoline-based frameworks.



Scheme 1. Examples of biologically active quinoline frameworks.

After the first formal synthesis of quinoline by Skraup,[23] several synthetic variations on the original Skraup synthesis, such as the Combes,[24] Conrad–Lympach,[25] Doebner von Miller,[26] Pfitzinger,[27] and Niementowski modifications,[28] and the Friedländer synthesis[29] have been developed. Recently, a modified-Friedländer reaction of 2-aminobenzylalcohol with an array of activated methylenes was repor-

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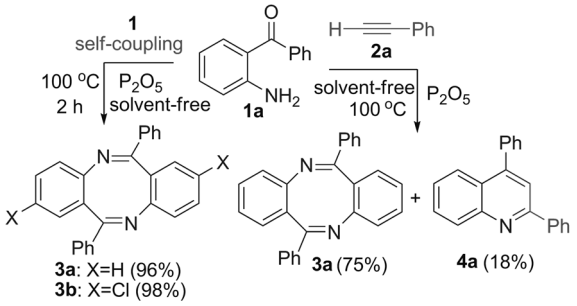
ted.[29j,k] Amongst these reported methodologies, the Friedländer annulation is a very simple, straightforward, and powerful tool, and is one of the "evergreen" methods of choice for researchers. Recently, quinolines have been synthesized by the treatment of 2-aminoarylcarbonyl compounds with alkynes through hydroamination of the alkyne followed by cyclodehydration.[30] In addition, different Lewis[31] and Brønsted[32] acids/bases, heterogeneous and solid-supported reagents,[33] ionic liquids,[34] and microwave irradiation[35] have also been utilized for the synthesis of quinoline derivatives. However, most of these methods suffered from limitations, such as low yield, poor selectivity, tedious work-up, the use of hazardous organic solvents, harsh reaction conditions,[36] multistep reactions,[37] large amounts of base,[38] expensive and/or harmful catalysts,[39] and the need for oxidants for the aromatization step[40] or other promoters/additives.[41] Therefore, more general, efficient, and viable routes with operational simplicity for the synthesis of quinoline derivatives are highly desirable, and would be of great relevance to both synthetic and medicinal chemists.

Because of the growing concern regarding the harmful effects of organic solvents on the environment and on the human body, solvent-free reactions[42] have aroused the attention of organic chemists owing to their more-efficient and less-labor-intensive methods. Because of their cost-effectiveness and waste-minimization, solvent-free methods have been used to modernize classical procedures by making them cleaner, safer, and easier to perform. Therefore, one pressing challenge facing organic chemists is to advance new processes that are not only efficient, selective, and high yielding but are also environmentally friendly. In recent years, indium chloride[43] has emerged as a highly efficient and effective Lewis acid catalyst that can promote a variety of chemical transformations chemo-, regio-, and stereoselectively, owing to its air- and water stability, operational simplicity, and remarkable ability to suppress side reactions in acid-sensitive substrates. We have been committed to the development of efficient synthetic procedures that mainly use solvent-free conditions.[44] In particular, we recently reported the $InCl_3$-catalyzed synthesis of important heterocycles, such as xanthenes,[44a–c] naphthopyranopyrimidines,[44d] chromene-2-thiones,[44e] chromeno[2,3-*d*]pyrimidinones,[44f] and diazabenzo[*b*]fluorenones[44f] under solvent-free conditions. Consequently, in light of other work in the literature, and as part of our ongoing efforts towards the development of new synthetic methods[44] for the synthesis of heterocycles, herein, we report the $InCl_3$-catalyzed one-pot coupling of 2-aminoarylketones with alkynes/active methylenes/α-oxoketene dithioacetals in acetonitrile as well as under solvent-free conditions to provide densely functionalized/annulated quinolines in high yields. $InCl_3$ not only makes the synthetic process clean, safe, and inexpensive, but also can provide various bioactive quinoline frameworks from the same 2-aminoaryl/alkylketones.

Results and Discussion

A survey of the literature revealed that there were no reports of the use of $InCl_3$ as a catalyst in the synthesis of quinoline derivatives by the coupling of 2-aminoaryl/alkyl ketones with alkynes/active methylenes/α-oxoketene dithioacetals, either in acetonitrile or under solvent-free conditions. To explore suitable reaction conditions, we began with the reaction of 2-aminobenzophenone (**1a**, 1.0 mmol) with phenylacetylene (**2a**, 1.2 mmol) in the presence of P_2O_5 (20 mol%) under solvent-free conditions at 100°C for 2 hours (monitored by TLC). Work-up of the reaction mixture afforded the unexpected 6,12-diphenyldibenzo[*b,f*]-[1,5]diazocine (**3**) in 75% yield, whilst the expected 2,4-disubstituted quinoline (**4a**) was obtained in only 18% yield (Scheme 2). The formation of compound **3** as the major



Scheme 2. Reaction of 2-aminobenzophenone (**1a**) with phenylacetylene (**2a**).

product was attributed to the self-coupling–cyclodehydration of compound **1a** in the presence of P_2O_5. To confirm the P_2O_5-catalyzed formation of compound **3**, 2-aminobenzophenone (**1a**) was heated in the presence of P_2O_5 (20 mol%) under solvent-free conditions at 100°C for 2 hours, thereby resulting in the formation of compound **3a** as the sole product in 96% yield. 2,8-Dichloro-6,12-diphenyldibenzo[*b,f*][1,5]diazocine (**3b**) exhibited hormone-like activity[45a] and was confirmed to be structurally identical to the reported compound[45] by single-crystal X-ray diffraction (Figure 1; also see the Supporting Information).[46]

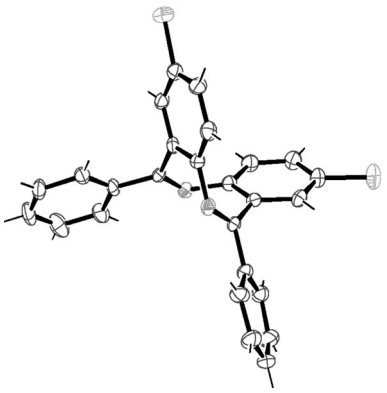


Figure 1. ORTEP of compound **3b**.

These results encouraged us to optimize the quinoline yield by changing the reaction conditions. Thus, the prototype reaction between compounds **1a** and **2a** was performed in the presence of different Lewis acids, such as $CuBr_2$, $NiCl_2$, $SnCl_4$, $AlCl_3$, and $InCl_3$ (20 mol% each) under solvent-free conditions. $CuBr_2$, $NiCl_2$, and $AlCl_3$ failed to produce the desired quinoline, even after 4 hours, whereas $SnCl_4$ triggered the reaction, but gave only trace amounts of the desired product (Table 1). To our delight, $InCl_3$ was an

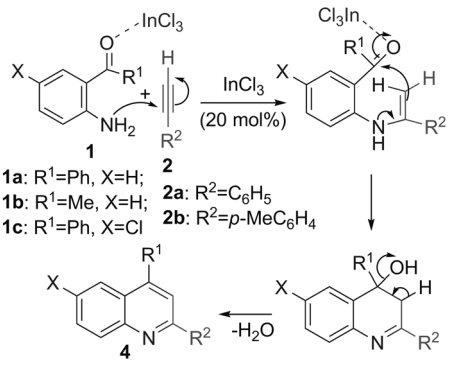
Table 1. Optimization of the catalyst.[a]

Entry	Catalyst [mol%]	Solvent	T [°C]	t [h]	Yield[b] [%]
1	P_2O_5 (20)	none	100	2	18
2	$CuBr_2$ (20)	none	100	4	–[c]
3	$NiCl_2$ (20)	none	100	4	–[c]
4	$SnCl_4$ (20)	none	100	4	trace
5	$AlCl_3$ (20)	none	100	4	–[c]
6	$InCl_3$ (20)	none	100	2.5	68
7	$InCl_3$ (20)	CH_3CN	82	3	93
8	$InCl_3$ (20)	EtOH	80	5	–[c]
9	$InCl_3$ (20)	THF	66	5	–[c]
10	$InCl_3$ (20)	toluene	110	5	81
11	$InCl_3$ (10)	CH_3CN	82	4	85
12	$InCl_3$ (30)	CH_3CN	82	3	90
13	P_2O_5 (20)	CH_3CN	82	3	45
14	$CuBr_2$ (20)	CH_3CN	82	6	–[c]
15	$NiCl_2$ (20)	CH_3CN	82	6	–[c]
16	$SnCl_4$ (20)	CH_3CN	82	6	trace
17	$AlCl_3$ (20)	CH_3CN	82	6	–[c]

[a] Reaction of 2-aminobenzophenone **1a** (1.0 mmol) with phenylacetylene **2a** (1.2 mmol). [b] Yield of isolated product. [c] No quinoline was formed.

effective catalyst for this reaction, thereby providing quinoline **4a** in 68% yield within 2.5 hours (Table 1, entry 6), together with the undesired product (**3a**) in 26% yield. Encouraged by this result, the effects of different solvents, such as acetonitrile, ethanol, tetrahydrofuran, and toluene, were also investigated in the presence of $InCl_3$ (20 mol%) with a view to increase the yield of quinoline. In ethanol and tetrahydrofuran, the reaction did not occur and the starting materials remained unreacted. In acetonitrile, the desired quinoline (**4a**) was obtained exclusively in 93% yield (Table 1, entry 7). Next, the $InCl_3$ loading was examined (Table 1, entries 11 and 12), and we found that 20 mol% of $InCl_3$ in acetonitrile provided the maximum yield in the minimum time. Furthermore, the catalysts P_2O_5, $CuBr_2$, $NiCl_2$, $SnCl_4$, and $AlCl_3$ were also investigated in acetonitrile. P_2O_5 catalyzed the reaction to furnish the quinoline, albeit in low yield, $CuBr_2$ and $NiCl_2$ were completely ineffective, and $SnCl_4$ provided only trace amounts of the desired quinoline (Table 1, entries 13–17). Thus, $InCl_3$ was clearly the catalyst of choice. The highest yield, cleanest reaction, and most-facile workup was achieved with 20 mol% $InCl_3$ in acetonitrile. The catalytic role of $InCl_3$ was evident from the fact that control experiments in the absence of $InCl_3$ did not afford the desired product.

Subsequently, with optimal conditions in hand, the scope and generality of this one-pot two-component coupling reaction was demonstrated by synthesizing a series of substituted quinolines by varying both the carbonyl and alkyne components (Schemes 3–5). 2-Aminoarylketones (**1**) and alkynes



Scheme 3. Synthesis of quinolines **4**.

(**2**) were well-tolerated under the optimized reaction conditions, thereby providing the corresponding quinolines (**4a**–**4d**) in 92–94% yield (Scheme 3, Table 2). The reactions

Table 2. Synthesis of quinolines **4a**–**4f**.

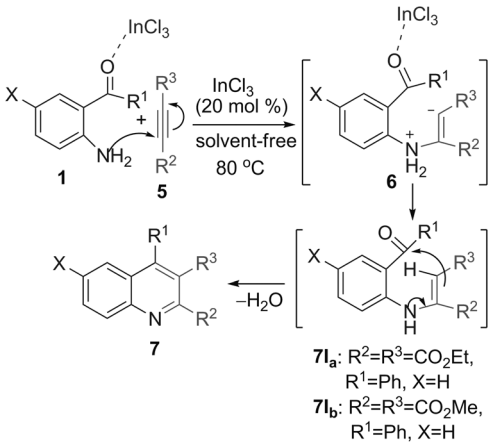
Entry	X	R^1	R^2	t [h]	Yield [%][a]
4a	H	C_6H_5	C_6H_5	3	93[b]
4b	H	C_6H_5	p-MeC_6H_4	3	92[b]
4c	Cl	C_6H_5	C_6H_5	3	94[b]
4d	Cl	C_6H_5	p-MeC_6H_4	3	93[b]
4e	H	Me	p-MeC_6H_4	3	93[c]
4f	H	Me	C_6H_5	3	92[c]

[a] Yield of isolated product. [b] Reaction performed in MeCN. [c] Reaction performed under solvent-free conditions.

were generally clean and no side-products, such as dihydroquinoline, were detected in the NMR spectra of the crude products. Surprisingly, when 2-aminobenzophenone (**1a**) was replaced with 2-aminoacetophenone (**1b**), the reaction did not proceed at all in acetonitrile and compound **1b** was recovered unconsumed. However, under solvent-free conditions, quinolines **4e** and **4f** were obtained in 93% and 92% yield, respectively (Table 2). This inconsistency may be due to the formation of the enol form of 2-aminoacetopheone (**1b**) in acetonitrile, which inhibited the progress of the reaction. Furthermore, when a terminal aliphatic alkyne (1-octyne) and an internal alkyne (1-phenyl-1-butyne) were used under the optimized conditions, the desired quinoline was not obtained, even in trace amounts. This result limits the scope of the reaction to some extent.

To further study the scope of this quinoline synthesis, the reactions of compound **1** with various internal alkynes (**5**) were examined under the optimized conditions, with a view to synthesize 2,3,4-trisubstituted quinolines. The expected quinolines (**7**) were obtained in good yield within 3 hours. The reaction between compounds **1** and **5** was also performed under solvent-free conditions in the presence of $InCl_3$ (20 mol%) at 80°C. Satisfyingly, quinolines **7a**–**7f**

were obtained exclusively in 92–97% yield within 50 minutes, except for compound **7g**, which was obtained in moderate yield (46%) after a longer reaction time (Scheme 4, Table 3). Coupling 2-aminoaryl/alkyl ketone **1** with compound **5** gave intermediate **6**, which underwent an $InCl_3$-mediated intramolecular cyclodehydration to yield the desired quinoline (**7**) in excellent yield. One attractive feature of this reaction was that we were able to isolate and characterize intermediates $\mathbf{7I_a}$ and $\mathbf{7I_b}$, when the reaction was performed at room temperature in the presence of 20 mol% $InCl_3$.[47,30f] The mechanism could be further rationalized from our experimental observations, as an aliphatic terminal alkyne (1-octyne) did not undergo the reaction, owing to the poor electrophilicity of the carbon center of the alkyne bearing the alkyl group, which was not sufficient enough for the nucleophilic attack. The internal alkyne (1-phenyl-1-butyne) also did not undergo the reaction because the carbanion, like intermediate **6**, became unstable owing to the presence of the electron-donating ethyl group. Although there have been a few reports where terminal aliphatic alkynes undergo this reaction in the presence of transition-metal Lewis acid catalysts, which played dual roles as a Lewis acid and a π-activator by coordinating to the acetylene bond,[30f–i] in our case, indium did not possess such π-activation capability. However, the reaction of compound **1** with an unsymmetrical internal alkyne (ethyl-3-phenylpropiolate) furnished the desired quinoline in low yield. In this case, compound **1** regioselectively attacked the carbon atom of the alkyne that contained the phenyl group because intermediate **6** was stabilized by an electron-withdrawing CO_2Et group.



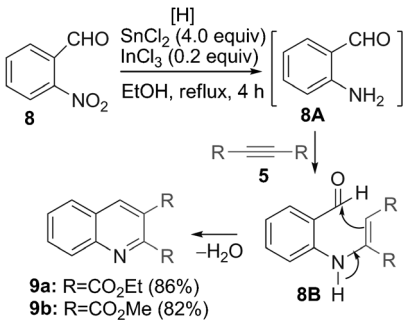
Scheme 4. Synthesis of quinolines **7**.

Table 3. Synthesis of quinolines **7a**–**7g**.

Entry	X	R^1	R^2	R^3	*t* [min]	Yield[a] [%]
7a	H	C_6H_5	CO_2Et	CO_2Et	50	94
7b	H	C_6H_5	CO_2Me	CO_2Me	50	94
7c	Cl	C_6H_5	CO_2Et	CO_2Et	50	97
7d	Cl	C_6H_5	CO_2Me	CO_2Me	50	96
7e	Cl	2-ClC_6H_4	CO_2Et	CO_2Et	50	92
7f	H	Me	CO_2Et	CO_2Et	50	93
7g	Cl	C_6H_5	C_6H_5	CO_2Et	210	46

[a] Yield of isolated product.

Furthermore, to expand the scope of this synthesis and to gain a greater insight into the reaction, we also performed the reaction of 2-nitrobenzaldehyde (**8**) with symmetrical alkyne **5** in the presence of $SnCl_2{\cdot}2H_2O$ and $InCl_3$ in ethanol. The reduction of compound **8** with $SnCl_2{\cdot}2H_2O$[48a,b] to 2-aminobenzaldehyde (**8A**) followed by reaction with compound **5** afforded quinoline (**9**) in good yield (Scheme 5).



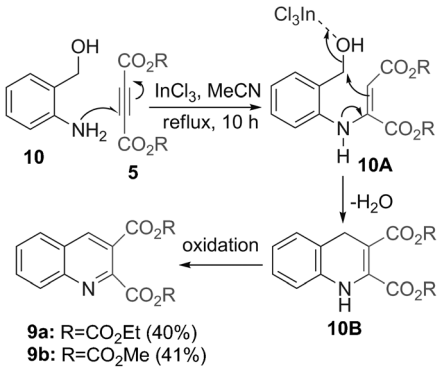
Scheme 5. Synthesis of quinolines **9**.

The regiochemistry of the reaction depended on the experimental conditions. The reaction proceeded faster and afforded higher yields in the presence of $InCl_3$, whilst in the absence of $InCl_3$, the desired quinoline (**9**) was obtained in poor yield along with the self-condensed product of compound **8A**.[49] Thus, $InCl_3$ clearly inhibited the formation of the self-condensed product of compound **8A**, which was highly prone to self-condensation, and promoted the formation of the desired quinoline (**9**). This was the first direct quinoline synthesis from the reaction of 2-nitrobenzaldehyde (**8**) with dialkyl acetylenedicarboxylates (**5**). Surprisingly, when compound **8** was treated with an unsymmetrical alkyne (*p*-tolyl acetylene) in the presence of $SnCl_2{\cdot}2H_2O$ and $InCl_3$, the desired quinoline was obtained in only 12% yield, thus limiting the scope of the reaction to some extent. The compound was characterized and found to be identical to the reported one.[48c]

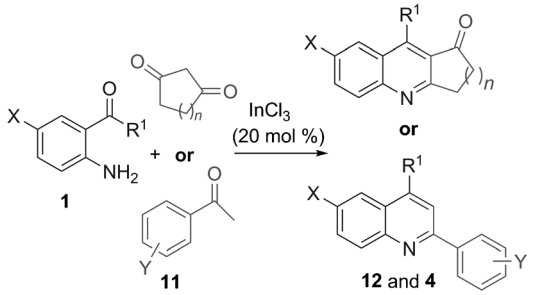
Inspired by these results, and keeping in mind the versatility of the $InCl_3$, we performed the reaction of 2-aminobenzylalcohol (**10**) with dialkyl acetylenedicarboxylates (**5**) in the presence of 20 mol% of $InCl_3$ in acetonitrile. However, the reaction was less efficient, and only afforded the desired quinolines (**9**) in moderate yield (Scheme 6).

The scope of this $InCl_3$-catalyzed procedure was further evaluated by performing the Friedländer reaction between compound **1** and cyclic/acyclic active methylene compounds (**11**), with a view to synthesizing annulated quinolines (**12**; Scheme 7).

Friedländer annulations are typically either carried out by refluxing an aqueous/alcoholic solution of the reactants in the presence of acid/base or by heating the mixture of reactants at 150–220 °C in the absence of a catalyst.[29] Herein,



Scheme 6. Synthesis of quinolines **9**.

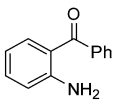
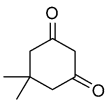
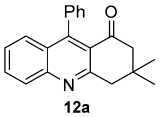
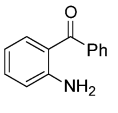
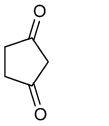
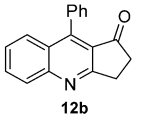
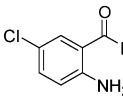
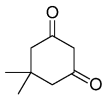
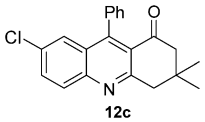
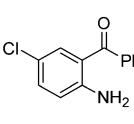
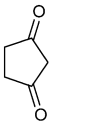
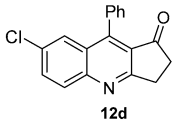
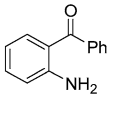
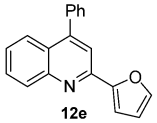
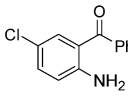
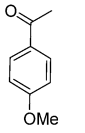
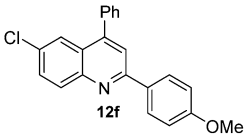
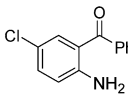
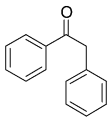
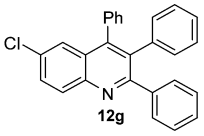
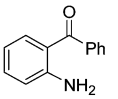
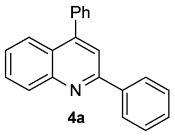
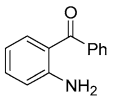
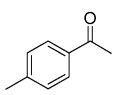
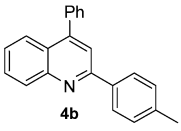
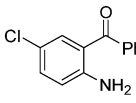
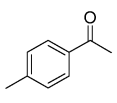
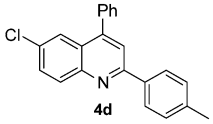
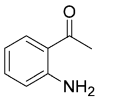
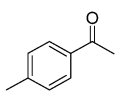
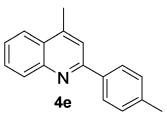
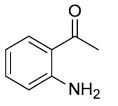
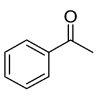
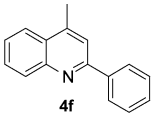


Scheme 7. Friedländer synthesis of quinolines **12** and **4**.

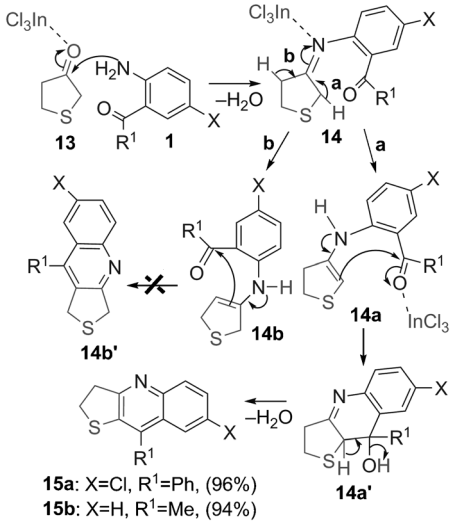
we report an efficient Friedländer annulation[50] promoted by $InCl_3$ under mild conditions, which overcomes the problems arising from the use of stoichiometric amounts of Brønsted and Lewis acidic or basic reagents. Thus, when 2-aminobenzophenone (**1a**, 1.0 mmol) was treated with dimedone (1.0 mmol) in the presence of 20 mol% of $InCl_3$ in acetonitrile, the annulated quinoline (**12a**) was obtained exclusively in 93% yield. To obtain a broad range of annulated quinolines (**12**), the tolerance of precursors **1** and **11** were investigated under the optimized conditions, and resulted in the formation of annulated/substituted quinolines (**12** and **4**) in excellent yield (Table 4, entries 1–10). Surprisingly, when 2-aminoacetophenone (**1b**) was used in the place of 2-aminobenzophenone (**1a**), no quinoline was observed; however, under solvent-free conditions, the reaction proceeded smoothly to give the desired quinolines (**4e** and **4f**) in quantitative yield (Table 4, entries 11 and 12).

With a variety of multifunctional, substituted, and annulated quinolines in hand, we successfully applied our method to the synthesis of thienoquinolines (**15**). Thienoquinolines are known to exhibit various biological activities.[17] The regioselectivity of the reaction could be rationalized by the mechanism depicted in Scheme 8. Presumably, the transformation was facilitated by the condensation of compound **1** with compound **13** to afford the imine intermediate **14**, which presumably underwent tautomerization through two different pathways (a and b). Route a furnished enamine **14a**, which underwent intramolecular regiospecific cyclodehydration through intermediate **14a′** to furnish quinolines

Table 4. Synthesis of annulated/substituted quinolines **12** and **4**.

Entry	2-Aminoaryl/alkylketone **1**	Active methylene **11**	Product	*t* [h]	Yield [%][a]
1			 **12a**	4	93[b]
2			 **12b**	3.5	94[b]
3			 **12c**	4	94[b]
4			 **12d**	3.5	95[b]
5			 **12e**	3	96[b]
6			 **12f**	3	95[b]
7			 **12g**	10	88[b]
8			 **4a**	3	95[b]
9			 **4b**	3	94[b]
10			 **4d**	3	96[b]
11			 **4e**	2.5	95[c]
12			 **4f**	2.5	96[c]

[a] Yield of isolated product. [b] Reaction performed in MeCN. [c] Reaction performed under solvent-free conditions.

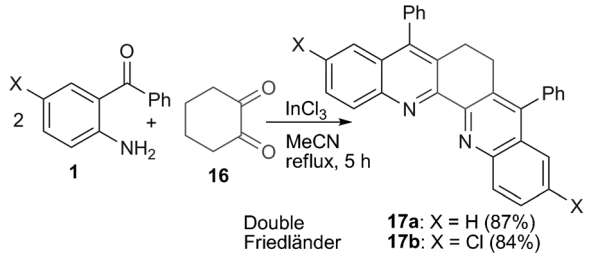


Scheme 8. Mechanism for the formation of thienoquinolines **15**.

15a and **15b** in 96 and 94% yields, respectively.[51] The observed regioselectivity was ascribed to the stabilization of enamine **14a** by conjugative interaction of the enamine group with sulfur, which was not possible for the regioisomeric **14b**. Route b may lead to regioisomeric enamine **14b**, which could provide quinoline **14b′**; compound **14b′** was not observed even in trace amounts during our investigation.

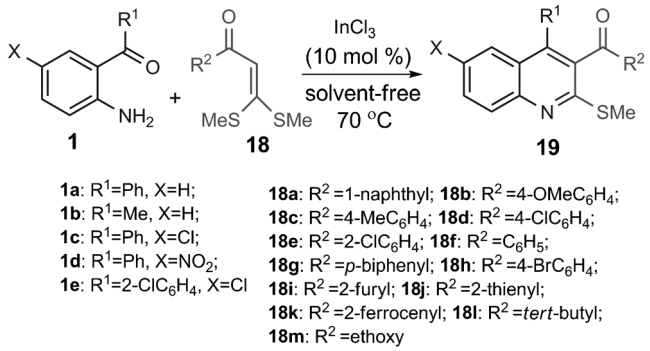
Not only, there are limited examples of double Friedländer annulations, but also they have been performed under harsh acidic/basic conditions. Herein, we performed the reaction of compound **1** (2.0 mmol) with 1,2-cyclohexanedione (**16**, 1.0 mmol) in acetonitrile in the presence of 20 mol% of $InCl_3$ to afford pentacyclic 5,8-diphenyl-6,7-dihydrodibenzo-[*b,j*][1,10]phenanthrolines (**17**) through double Friedländer annulation[52] in 84–87% yield (Scheme 9). Compounds **17** are used as receptors, owing to their interesting chelating capacity,[52c] and are widely used to develop dye-sensitized nanocrystalline metal–oxide solar cells.[52d,e]

Furthermore, to make this century-old Friedländer reaction more practical and general, we attempted to develop a Friedländer annulation that uses α-oxoketene dithioacetals as an electrophilic partner instead of enolizable carbonyl compounds. α-Oxoketene dithioacetals are versatile intermediates in organic synthesis and have been extensively used in the construction of various five- and six-membered



Scheme 9. Synthesis of dibenzo[b,j][1,10]phenanthrolines **17**.

heterocycles.[53] There are only few reports on the synthesis of quinolines using ketene dithioacetals.[54] α-Oxoketene dithioacetals **18a**–**18m** were prepared according to a literature procedure.[55] Therefore, we envisaged that a tandem reaction between 2-aminoarylketones (**1**) and α-aroylketene dithioacetals (**18**) would furnish quinolines **19** (Scheme 10).



Scheme 10. Friedländer synthesis of quinolines **19**.

We began with a typical reaction of 2-aminobenzophenone (**1a**) and 3,3-bis(methylthio)-1-naphthalen-1-yl-propenone (**18a**) under optimized conditions (20 mol% $InCl_3$, CH_3CN), which provided the desired compound in 75% yield. When the reaction was carried out in the presence of 20 mol% of $InCl_3$ under solvent-free conditions, the desired quinoline was formed in 88% yield. Furthermore, when the $InCl_3$ loading was decreased from 20 mol% to 10 mol%, the yield of the quinoline increased to 90%. Finally, the reaction temperature was also examined and 70°C was found to be the optimum temperature, as it afforded the best compromise between reaction profile and reaction rate. Thus, the highest yield, cleanest reaction, and most-facile work-up was achieved with 10 mol% of $InCl_3$ at 70°C under solvent-free conditions.

Under these optimized conditions, we studied the substrate scope and generality of this one-pot Friedländer reaction by synthesizing a small library of highly functionalized quinolines (**19a**–**19v**) in excellent yields (Scheme 10, Table 5). Notably, a wide range of 2-aminoarylketones (**1a**–**1e**) and α-oxoketene dithioacetals (**18a–18m**) were well-tolerated under the optimized reaction conditions and furnished a broad spectrum of densely functionalized quinolines (**19**). Even extremely electron-rich aromatic α-oxoketene dithioacetals, such as compounds **18i** and **18j**, reacted smoothly. In addition to the incorporation of aryl, heteroaryl, and aliphatic substituents, the η^5-ferrocenyl group was also tolerated by this procedure (Table 5, entry 20).

Structural determination of all of the quinoline derivatives (**19a**–**19v**) was performed from their ^1H and ^{13}C NMR, IR, and MS data. We unequivocally established the regiochemistry of two representative compounds (**19a** and **19c**) by single-crystal X-ray diffraction analysis (Figure 2).[46]

On the basis of these above results, the probable mechanistic pathway for the formation of compound **19** is shown

Table 5. Scope of the synthesis of quinolines **19**.

Entry	X	R^1	R^2	Product	Yield[a] [%]
1	H	C_6H_5	1-naphthyl	**19a**	90
2	H	CH_3	1-naphthyl	**19b**	92
3	H	C_6H_5	4-$OMeC_6H_4$	**19c**	92
4	Cl	C_6H_5	4-$OMeC_6H_4$	**19d**	95
5	H	C_6H_5	4-MeC_6H_4	**19e**	91
6	H	CH_3	4-MeC_6H_4	**19f**	86
7	Cl	C_6H_5	4-ClC_6H_4	**19g**	93
8	Cl	2-ClC_6H_4	4-ClC_6H_4	**19h**	81
9	H	C_6H_5	2-ClC_6H_4	**19i**	91
10	H	CH_3	2-ClC_6H_4	**19j**	82
11	Cl	C_6H_5	C_6H_5	**19k**	92
12	Cl	2-ClC_6H_4	C_6H_5	**19l**	84
13	H	C_6H_5	*p*-biphenyl	**19m**	89
14	Cl	C_6H_5	*p*-biphenyl	**19n**	88
15	Cl	C_6H_5	4-BrC_6H_4	**19o**	90
16	H	C_6H_5	2-furyl	**19p**	88
17	Cl	C_6H_5	2-furyl	**19q**	90
18	Cl	C_6H_5	2-thienyl	**19r**	89
19	NO_2	C_6H_5	2-thienyl	**19s**	84
20	Cl	C_6H_5	2-ferrocenyl	**19t**	83
21	Cl	C_6H_5	*t*Bu	**19u**	92
22	Cl	C_6H_5	OEt	**19v**	91

[a] Yield of isolated product.

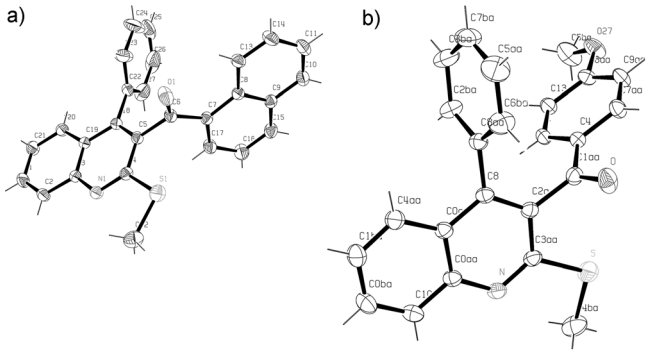
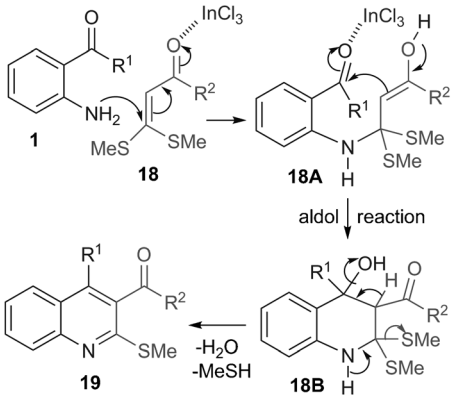


Figure 2. ORTEP of compounds **19a** and **19c**.

in Scheme 11. It is conceivable that nucleophilic attack of the amine group of compound **1** on the methylthio-substituted β-carbon of compound **18** gives intermediate **18A**, which then undergoes an intramolecular aldol reaction to give intermediate **18B**. Upon subsequent loss of H_2O and MeSH, intermediate **18B** affords the desired quinoline (**19**).



Scheme 11. Plausible mechanism for the synthesis of quinolines **19**.

Conclusions

Structurally diverse quinolines have been synthesized by the one-pot two-component regioselective coupling of 2-aminoarylketones with alkynes/active methylenes/α-oxoketene-dithioacetals promoted by $InCl_3$ in acetonitrile as well as under solvent-free conditions; these reactions proceeded by the hydroamination–hydroarylation of alkynes, and the Friedländer annulation of active methylene compounds and α-oxoketene dithioacetals. $InCl_3$ was used in all of the reactions and no co-catalyst or activator was needed. This method not only provides an excellent complement to substituted/annulated quinoline synthesis, but also avoids the use of hazardous acids or bases and harsh reaction conditions. The merits of this procedure are its mild reaction conditions, high selectivities, excellent yields, ease of purification, economic viability, and ready availability of the catalyst and starting materials. In addition to its simplicity and selectivity, this reaction can tolerate a variety of functional groups and is a viable alternative to the currently used procedures.

Experimental Section

General

All starting materials were commercially available and used as received without further purification. α-Oxoketene dithioacetals (**18**) were prepared according to a literature procedure.[55] Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} precoated plates. IR spectra were measured in KBr, and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on NMR spectrometers operating at 300 and 75.5 MHz, respectively. Chemical shifts (δ) are given in parts per million (ppm) using the residue solvent peaks as reference relative to TMS. *J* values are given in Hz. Mass spectra were recorded using electrospray ionization (ESI) mass spectrometry. C, H, and N analysis was performed by the microanalytical laboratory. The melting points are uncorrected.

*General Procedure for the Synthesis of 6,12-Diphenyldibenzo[b,f][1,5]diazocine (**3**)*

A mixture of 2-aminobenzophenone (**1a**; 1.0 mmol) and P_2O_5 (0.2 mmol) in a 25 mL round-bottomed flask was heated at 100 °C for 2 h. After completion of the reaction (monitored by TLC), water (15 mL) was added and the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to afford the pure product (**3**).

*General Procedure for the Synthesis of 2,4-Disubstituted quinolines (**4**)*

$InCl_3$ (0.2 mmol) was added to a mixture of compounds **1** (1.0 mmol) and **2** (1.2 mmol) either in CH_3CN (Table 2, **4a**–**4d**) or under solvent-free conditions (Table 2, **4e** and **4f**). The reaction mixture was heated to reflux in CH_3CN (or at 100 °C under solvent-free conditions) for the stipulated period of time. After completion of the reaction (monitored by TLC), the solvent was evaporated (for the reaction in CH_3CN). Then, water (15 mL) was added and the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic extract was washed with brine

and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuo and the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:49) to afford the pure 2,4-disubstituted quinoline (**4**).

*General Procedure for the Synthesis of 2,3,4-Trisubstituted Quinolines **7***

A mixture of compound **1** (1.0 mmol), dialkyl acetylenedicarboxylate **5** (1.2 mmol), and $InCl_3$ (0.2 mmol) was heated at 80 °C in a 25 mL round-bottomed flask for the stipulated period of time (Table 3). After completion of the reaction (monitored by TLC), water (15 mL) was added and the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 3:47) to afford the pure 2,3,4-trisubstituted quinoline (**7**).

*General Procedure for the Synthesis of Quinoline **9** from o-Nitrobenzaldehyde*

A mixture of *o*-nitrobenzaldehyde (**8**, 1.0 mmol), dialkyl acetylenedicarboxylate **5** (1.2 mmol), $SnCl_2{\cdot}2H_2O$ (4.0 mmol), $InCl_3$ (0.2 mmol), and EtOH (5 mL) was heated to reflux in a 25 mL round-bottomed flask with continuous stirring for 3.5 h. After completion of the reaction (monitored by TLC), the solvent was evaporated. Then water (15 mL) was added and the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuo and the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 3:17) to give the pure product.

*General Procedure for the Synthesis of Quinoline **9** from o-Aminobenzylalcohol*

$InCl_3$ (0.2 mmol) was added to a mixture of *o*-aminobenzylalcohol (**10**, 1.0 mmol) and dialkyl acetylenedicarboxylate **5** (1.2 mmol) in CH_3CN (5 mL) in a 25 mL round-bottomed flask, and the mixture was heated to reflux for 10 h with continuous stirring. After completion of the reaction (monitored by TLC), the solvent was evaporated. Then, water (15 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 3:17) to give the pure product.

*General Procedure for the Synthesis of Quinolines **12** and **15***

A mixture of 2-aminoaryl/alkyl ketone **1** (1.0 mmol), activated methylene **11**/**13** (1.0 mmol), and $InCl_3$ (0.2 mmol) either in CH_3CN (5 mL; Scheme 8, Table 4, entries 1–10) or under solvent-free conditions (Table 4, entries 11 and 12) was heated in a 25 mL round-bottomed flask for the time period mentioned in Table 4. After completion of the reaction (monitored by TLC), the solvent was evaporated. Then water (15 mL) was added and the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the crude residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane) to afford the pure product (**12**/**15**).

*General Procedure for the Synthesis of 5,8-Diphenyl-6,7-dihydrodibenzo[b,j][1,10]-phenanthrolines **17***

A mixture of *o*-aminobenzophenone (**1**, 2.0 mmol), 1,2-cyclohexanedione (**16**, 1.0 mmol), $InCl_3$ (0.2 mmol), and CH_3CN (5 mL) was heated to reflux in a 25 mL round-bottomed flask with continuous stirring for 5 h. After completion of the reaction (monitored by TLC), the solvent was evaporated. Then, water (15 mL) was added and the reaction mixture was extracted with $CHCl_3$ (3×10 mL). The combined organic extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 3:7) to afford the pure product (**17**).

*General Procedure for the Synthesis of Quinolines **19***

A mixture of 2-aminoaryl/alkyl ketone **1** (1.0 mmol) and α-oxoketene dithioacetal **18** (1.0 mmol) was heated at 70 °C in the presence of $InCl_3$ (10 mol%, 0.1 mmol, 0.022 g) for the stipulated period of time (0.5–2.0 h) until the reaction had been completed (monitored by TLC). The mixture was treated with water (20 mL) and extracted with EtOAc (1×20 mL). The combined organic extract was washed with brine (1×20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give the crude product, which was either purified by crystallization from EtOH or by column chromatography on silica gel (EtOAc/*n*-hexane, 1:49).

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