Gold(III) Chloride Catalyzed Intermolecular Dimerization of 2-Ethynylanilines: Synthesis of Substituted Quinolines

C. Praveen, S. Jegatheesan, P. T. Perumal*

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India
Fax +91(44)24911589; E-mail: ptperumal@gmail.com

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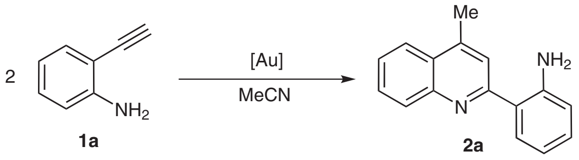
Abstract: An unprecedented gold(III)-catalyzed intermolecular dimerization of 2-ethynylanilines possessing terminal triple bond offers a general synthetic pathway to a wide range of highly substituted quinolines.

Key words: 2-ethynylanilines, terminal alkyne, gold(III), intermolecular dimerization, substituted quinolines

The prevalence of quinolines[1] in numerous natural products that exhibit a wide range of pharmacological activities, such as antimalarial, anti-inflammatory, antineoplastic, antifungal, antiseptic/anti-infective, and analgesic properties,[2] has led to a continued interest in the practical synthesis of this class of heterocyclic compounds. They also find application in material science,[3] bioorganometallic processes,[4] and agrochemicals and effect chemicals such as dyestuffs and corrosion inhibitors.[5] Thus it is not surprising that numerous pathways for the synthesis of quinolines have been developed. Among various synthetic strategies,[6] catalytic transformation by means of transition-metal catalysts is one of the modern approaches for the synthesis of substituted quinoline derivatives. These include, rhodium-catalyzed condensation of *o*-aminophenylboronates with α,β-unsaturated ketones,[7a] gold-catalyzed cyclization of propargyl amines,[7b] palladium-catalyzed chlorimination of imidoyl chorides,[7c] $[Cp^*Fe(CO)_2]_2$-catalyzed reductive cyclization of *o*-nitro-substituted Baylis–Hillman acetates,[7d] iridium-catalyzed condensation of 2-aminobenzyl alcohol with ketones,[7e] indium-catalyzed microwave synthesis involving phenylacetylene and 2′-aminoacetophenones,[7f] cobalt-catalyzed rearrangement of *N*,*N*-diallylanilines,[7g] palladium-catalyzed multicomponent synthesis,[7h] and rhodium-catalyzed coupling–cyclization of *N*-aryltrifluoroacetimidoyl chlorides with alkynes.[7i] On the other hand, due to the unique ability to activate carbon–carbon multiple bonds, the use of gold catalysts plays an important role in modern transition-metal catalysis.[8] As part of our ongoing interest in gold-catalyzed organic reactions,[9] we have previously reported, gold(I)-catalyzed cycloisomerization of 2-ethynylanilines possessing internal triple bonds[9a] leading to indole derivatives. Recently, Sakai et al. reported a novel method for the synthesis of substituted quinolines by $InBr_3$-catalyzed dimerization of 2-ethynylanilines.[10] However, it was limited to specific substrate classes, stoichiometric use of $InBr_3$, and longer reaction time. To circumvent such substrate limitation, use of stoichiometric amount of catalyst, long duration of reaction time, and enhance the scope of the reaction, we have elected to investigate catalytic amount of gold salts for this unusual dimerization. We realized that 2-ethynylaniline possessing a terminal triple bond might undergo dimerization in the presence of a gold catalyst. Herein we wish to report, gold(III)-catalyzed intermolecular dimerizaton of 2-ethynylanilines leading to highly substituted quinolines.

The 2-ethynylanilines required for this methodology are readily prepared by the base-effected desilylation[11] of 2-(trimethylsilylethynyl)aniline, which in turn can be prepared by the Sonogashira coupling[12] of 2-iodoanilines[13] with ethynyltrimethylsilane. Initial studies were directed toward finding a general set of reaction conditions that could be applied to a wide variety of substrates. To begin our study, we examined the reaction of 2-ethynylaniline (**1a**) with several gold catalysts in dry acetonitrile[14] as summarized in Scheme 1 and Table 1.



Scheme 1 Gold-catalyzed dimerization of 2-ethynylaniline (**1a**) under various reaction conditions

The use of 5 mol% of gold(I) complexes like Ph_3PAuCl, Et_3PAuCl, and Me_3PAuCl did not show the reactivity for this transformation (entries 1–3). The use of AuCl induced the formation of indole exclusively,[15] and the quinoline product was formed only in trace amount (entry 4). The use of $AuBr_3$ resulted in the formation of only 10% of product (entry 5). Treatment of **1a** with 5 mol% of $AuCl_3$ afforded the quinoline product **2a** in 30% yield (entry 6). Gratifyingly, the use of 10 mol% of AgOTf as a cocatalyst along with 5 mol% of $AuCl_3$ afforded the product in high yield (entry 7). However, when the same reaction was carried out at reflux temperature, the reaction went into completion in 1 hour (entry 8). Again, when the same reaction was tested with $AuCl_3$ (5 mol%) to AgOTf (15 mol%) in a 1:3 ratio, it resulted in a very good yield of the product (entry 9), but not higher than that tested with a 1:2 ratio (entry 8). But the use of AgOTf alone did not led to any

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Table 1 Effect of Different Gold Catalysts on the Intermolecular Dimerization of 2-Ethynylaniline (**1a**)

Entry	Catalyst (mol%)	Yield (%)[a]
1	Ph_3PAuCl (5)	–
2	Me_3PAuCl (5)	–
3	Et_3PAuCl (5)	–
4	AuCl (5)	10[b]
5	$AuBr_3$ (5)	18
6	$AuCl_3$ (5)	30
7	$AuCl_3$ (5)/AgOTf (10)	65
8	$AuCl_3$ (5)/AgOTf (10)	89[c]
9	$AuCl_3$ (5)/AgOTf (15)	82[c]
10	AgOTf (10)	–
11	$AuCl_3$ (5)/$AgBF_4$ (10)	58[c]
12	$AuCl_3$ (5)/$AgSbF_6$ (10)	66[c]
13	$AuCl_3$ (5)/$AgOCOCF_3$ (10)	38[c]
14	$AuCl_3$ (5)/AgOAc (10)	35[c]
15	AgCl (10)	–
16	no catalyst	–

[a] Isolated yield.

[b] Indole was obtained as the major product.

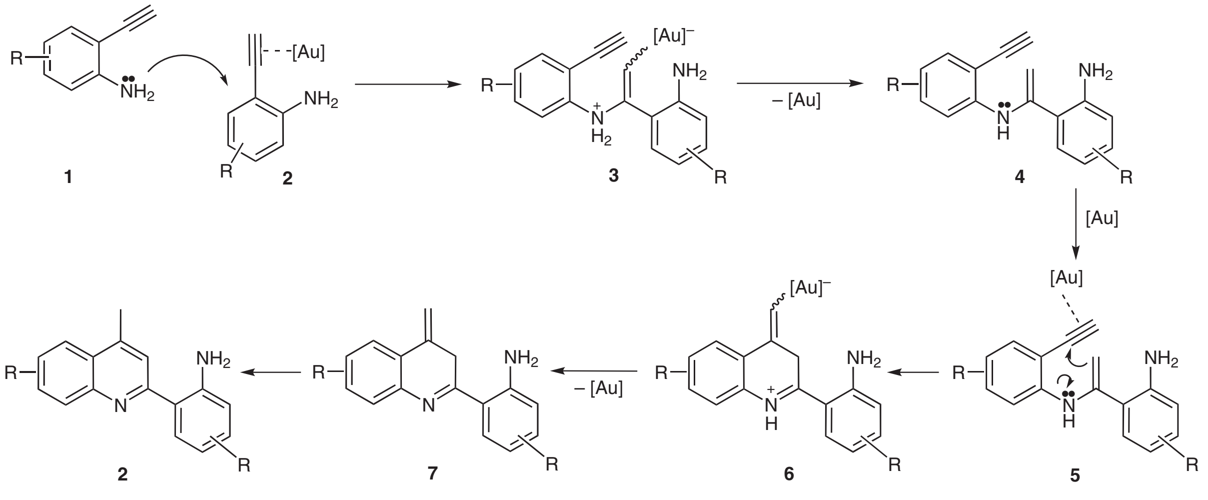
[c] The reaction was carried out at reflux temperature.

product formation at all (entry 10). This observation revealed that neither $AuCl_3$ nor AgOTf alone led to product formation, rather a combination of both $AuCl_3$ and AgOTf effectively catalyses this process to higher yields of product.[16] The use of other silver salts as cocatalysts resulted in product formation albeit in moderate yields (entry 11–14) and none of them gave better yield than AgOTf. Finally, the reaction in the presence of catalytic amount of AgCl and the absence of any catalyst does not afford the product at all (entries 15 and 16, respectively). In order to make all the experiments comparable in Table 1 (entries 1–3, 5–7, 9, 14, and 15) were also carried out at reflux temperature and observed no improvement in terms of product formation.

Since a combination of 5 mol% of $AuCl_3$ and 10 mol% of AgOTf (Table 1, entry 8) provided a higher yield for the parent system compared with other catalysts, this procedure was chosen to test the scope of the dimerization process for other substrates.[17] Under this reaction conditions, substrates possessing various functionalities such as nitro, ester, ether, and cyano were tolerated well, affording the corresponding quinoline derivatives in good yields (Table 2).

The result revealed that the yield of the products were independent of the groups attached on the periphery of the substrate, since both electron-withdrawing as well as electron-releasing substrates gave almost the same yield. Moreover, all reactions went into completion within one hour. Thus, these reaction conditions appeared to be far more efficient than those previously used indium procedures, which requires high reaction time (>24 h).[10] Furthermore, the beneficial effect of this new methodology is the dimerization of substrate **1o** leading to naphthyridine **2o**, albeit in moderate yield. However, in contrast $InBr_3$ failed in the dimerization of such substrates.

A tentative mechanistic pathway for the gold(III)-catalyzed dimerization of 2-ethynylaniline is proposed in Scheme 2. The alkyne coordinates to gold(III) to form π-complex **2**, which enhances the electrophilicity of the alkyne. Subsequent nucleophilic attack of the amino group of the other molecule of 2-ethynylaniline **1** affords gold–vinylidene[18] intermediate **3**. Protonation of the intermediate **3** with the proton on the ammonium gives the neutral enamine intermediate **4** and regenerate the gold catalyst. Gold again activates the intermediate **4** to form intermediate **5**, which undergoes cyclization to form the intermediate **6**. Again protonation of the vinyl–gold intermediate **6** with the proton on the ammonium gives intermediate **7**, which upon subsequent rearrangement affords the product **2**.



Scheme 2 Tentative mechanism for the gold(III)-catalyzed dimerization of 2-ethynylaniline

Table 2 Gold-Catalyzed Synthesis of Quinolines via Dimerization of 2-Ethynylanilines[a]

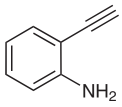
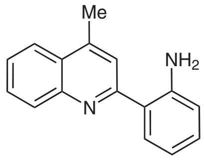
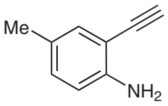
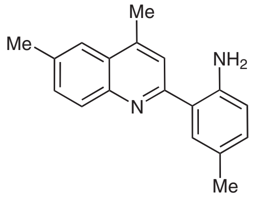
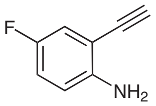
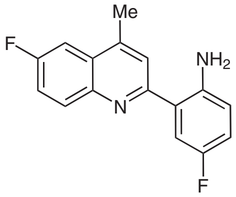
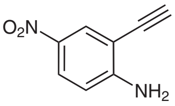
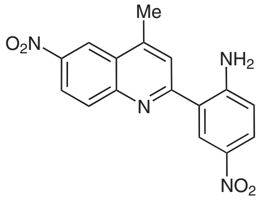
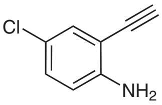
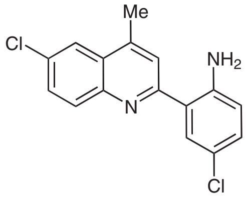
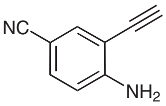
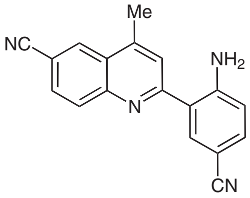
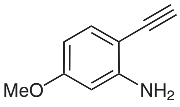
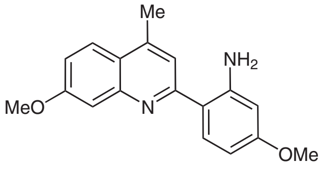
Entry	2-Ethynylaniline	Substituted quinoline[b]	Time (min)	Yield (%)[c]
1	 **1a**	 **2a**	20	89
2	 **1b**	 **2b**	20	84
3	 **1c**	 **2c**	45	74
4	 **1d**	 **2d**	45	78
5	 **1e**	 **2e**	30	73
6	 **1f**	 **2f**	30	76
7	 **1g**	 **2g**	40	79

Table 2 Gold-Catalyzed Synthesis of Quinolines via Dimerization of 2-Ethynylanilines[a] (continued)

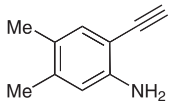
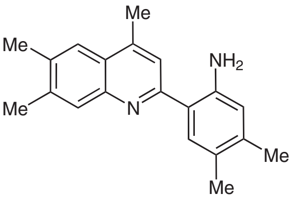
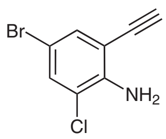
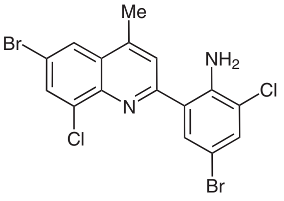
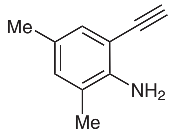
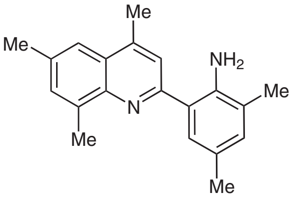
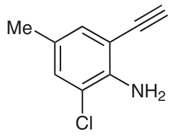
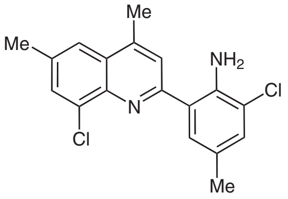
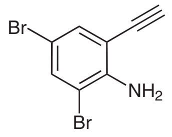
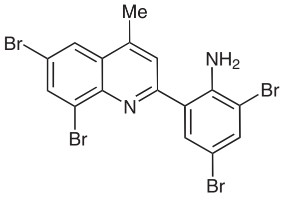
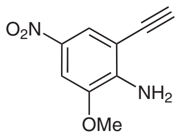
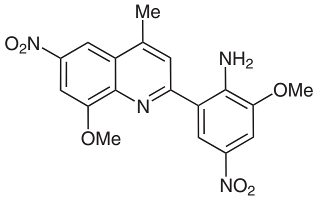
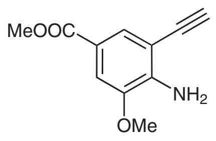
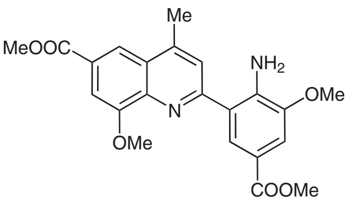
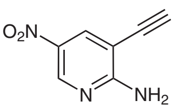
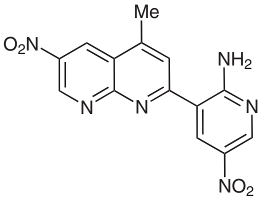
Entry	2-Ethynylaniline	Substituted quinoline[b]	Time (min)	Yield (%)[c]
8	 **1h**	 **2h**	25	86
9	 **1i**	 **2i**	30	77
10	 **1j**	 **2j**	25	78
11	 **1k**	 **2k**	40	75
12	 **1l**	 **2l**	30	88
13	 **1m**	 **2m**	40	81
14	 **1n**	 **2n**	35	85

Table 2 Gold-Catalyzed Synthesis of Quinolines via Dimerization of 2-Ethynylanilines[a] (continued)

Entry	2-Ethynylaniline	Substituted quinoline[b]	Time (min)	Yield (%)[c]
15	 **1o**	 **2o**	55	48

[a] All reactions were carried out at reflux temperature in MeCN solvent using 5 mol% of $AuCl_3$ and 10 mol% of AgOTf under nitrogen atmosphere.

[b] All products were characterized by IR, ^{1}H NMR, ^{13} C NMR, and MS.

[c] Isolated yield.

In summary, a catalytic system of $AuCl_3$/AgOTf effects the dimerization of 2-ethynylanilines leading to polysubstituted quinolines in good to excellent yield. This protocol is amenable to substrates possessing functionalities such as nitro, ether, cyano, ester, and heteroaromatic exhibiting good functional-group tolerance. No solvent extraction, the safe catalyst, and short reaction time are some of the noteworthy advantages of this protocol. Further synthetic applications of this novel dimerization to more complex heterocyclic ring systems are currently under investigation.

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(17) **General Procedure for the Gold-Catalyzed Dimerization of 2-Ethynylanilines 2a–o; Representative Procedure for 2,4-Dibromo-6-(6,8-dibromo-4-methyl-2-quinolinyl)-phenylamine (2l, Table 2, Entry 12)**
To a mixture of $AuCl_3$ (27.57 mg, 0.09 mmol) and AgOTf (46 mg, 0.181 mmol) under N_2 was added dry MeCN (2 mL) and stirred for 15 min at 25 °C. To the mixture was added a solution of 2,4-dibromo-6-ethynylaniline (**1l**, 500 mg, 1.81 mmol) in dry MeCN (2 mL) at 25 °C, and the whole was gradually warmed up to reflux temperature and stirred for the specified time (Table 2). After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and purified by column chromatography over silica gel (100–200 mesh) to afford pure product 2,4-dibromo-6-(6,8-dibromo-4-methyl-2-quinolinyl)phenylamine(**2l**) as a yellow solid; mp 186–188 °C. IR (KBr): 3751, 3473, 2956, 2430,1457, 766 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.51$ (s, 3 H), 4.12 (br s, 2 H), 7.10 (d, 1 H, $J = 2.3$ Hz), 7.65 (d, 1 H, $J = 2.2$ Hz), 8.14 (d, 1 H, $J = 2.3$ Hz), 8.19 (d, 1 H, $J = 2.3$ Hz), 8.71 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 26.9$, 109.2, 110.1, 120.7, 124.7, 126.6, 126.7, 129.9, 131.4, 132.1, 134.9, 136.0, 141.6, 143.2, 152.1, 162.8. MS (ESI+): $m/z = 551$ $[M^+ + H]^+$, 553 $[M^{2+} + H]^+$, 555 $[M^{4+} + H]^+$. Anal. Calcd for $C_{16}H_{10}Br_4N_2$: C, 34.95; H, 1.83; N, 5.09. Found: C, 35.07; H, 1.78; N, 5.00.

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