Gold-Catalyzed Benzannulation of Electronically Rich/Rich and Deficient/Deficient Oxoalkynes with Alkynes

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Abstract: Two different strategies have been developed to perform the gold-catalyzed benzannulation of both electron-rich pyridine containing oxoalkynes with electron-rich alkynes as well as electron-deficient pyridine containing oxoalkynes with electron-deficient alkynes. The benzannulation between electron-rich oxoalkynes with electron-rich alkynes proceeds in the presence of highly electron-deficient gold catalysts, whereas using catalytic amount of alcohol benzannulation was performed efficiently between electron-deficient oxoalkynes with electron-deficient alkynes.

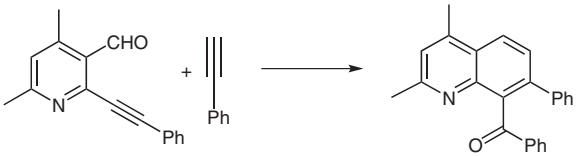
Key words: gold catalysis, homogeneous catalysis, benzannulation, cycloaddition, Lewis acids

The transition metal-catalyzed electrophilic activation of alkynes towards intramolecular addition of heteronucleophiles has attracted increasing attention of the synthetic community as a useful method for the preparation of diverse heterocyclic compounds.[1] In particular, it has been observed that $AuCl_3$ catalyzes the formation of both carbon–carbon and carbon–hetero atom bonds thereby behaving as an effective Lewis acid.[2,3] One of the pioneering examples of such reactions include benzannulation between *o*-alkynylbenzaldehydes and alkynes, and this has been developed extensively by the research groups of Yamamoto, Dyker, and others.[4] As an extension of this work, we have recently reported the homogeneous gold-catalyzed formal [4+2] benzannulation between pyridine containing oxoalkynes and alkynes, which leads to highly substituted quinoline and isoquinoline derivatives.[5]

In the methodology described in that paper, it was observed that the electron-rich azaisobenzopyrilium intermediates[6] generated from oxoalkynes **1a**–**d** react with electron-poor dienophiles, for example, dimethyl acetylenedicarboxylate and methyl propiolate, and electron-poor azaisobenzopyrylium intermediates generated from oxoalkyne **4** react with electron-rich dienophiles, for example, phenylacetylene, 4-*N*,*N*-dimethylaminophenylacetylene, etc., as would be expected on the basis of frontier molecular orbital (FMO) considerations (Scheme 1). From the synthetic point of view, one limitation of our method is that it does not allow formation of benzannulation products, which may be obtained from the reaction of electron-rich oxoalkynes with electron-rich alkynes or from the reaction of electron-deficient oxoalkynes with electron-deficient alkynes (mismatching on the basis of FMO). Indeed, the reaction of electron-rich oxoalkyne **1a** with phenylacetylene or diphenylacetylene does not furnish the benzannulation products, for example, **3f** or **3g**; similarly, the reaction of electron-deficient oxoalkyne **4** with dimethyl acetylenedicarboxylate or methyl propiolate does not furnish the benzannulation products **6d** or **6e** (Scheme 1). In connection with our ongoing work on transition metal-catalyzed organic transformations,[5,7] we now report two different strategies for the benzannulation of both rich/rich and deficient/deficient oxoalkynes with alkynes not available by our previously reported protocol.[5]

To extend our benzannulation methodology for rich/rich systems our idea was to make electron-deficient azaisobenzopyrylium auric ate complexes via coordination of electron-rich oxoalkynes with highly electron-deficient gold complexes. Gold salts having noncoordinating counterions (like OTf^-, BF_4^-, PF_6^-, SbF_6^-, etc.) are highly electron-deficient compared to gold chlorides.[8] Thus, usage of such highly electron-deficient gold salts might allow formation of electron-deficient azaisobenzopyrilium auric ate complexes from otherwise electron-rich oxoalkynes.

Table 1 Reaction of **1a** with Phenylacetylene Under Various Catalytic Systems[a]



1a **3f**

Entry	Catalytic system	Yield (%)[b]
1	$AuCl_3$	0
2	$AuCl_3$/AgOTf	11
3	$AuCl_3$/$AgSbF_6$	74
4	$AuCl_3$/$AgBF_4$	37
5	$AuCl_3$/$AgPF_6$	45
6	$AgSbF_6$	0

[a] All reactions were performed using **1a** (0.2 mmol) and phenylacetylene (0.4 mmol) in the presence of a combination of $AuCl_3$ (3 mol%) and silver salt (9 mol%), except for entries 1 and 6, in 1,2-dichloroethane (4 mL) at r.t. for 24 h.
[b] Isolated yield.

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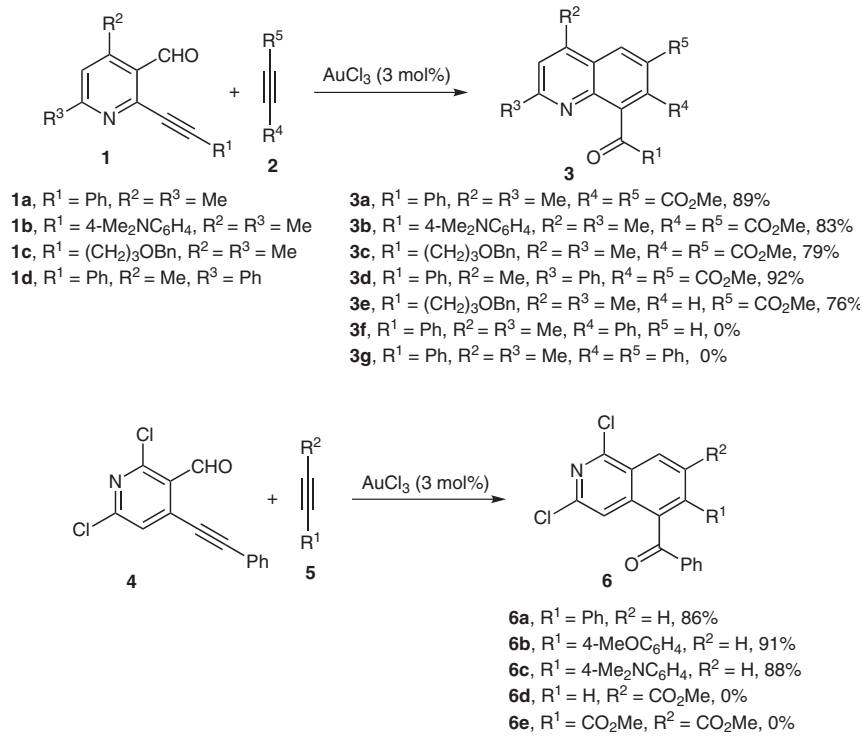
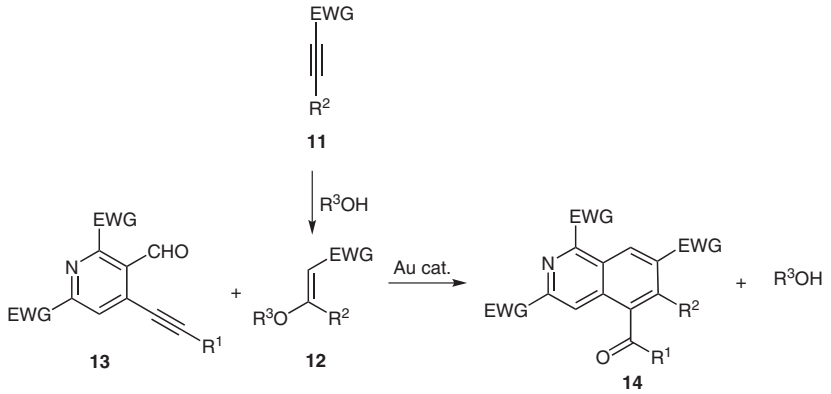


Scheme 1 Gold-catalyzed benzannulation of pyridine containing oxoalkynes with alkynes

Under these conditions, the electron-deficient azaisobenzopyrilium auric ate complexes thus formed may react with electron-rich alkynes following the inverse electron demand Diels–Alder reaction.

To test the feasibility of our idea, compound **1a**[9] (electron-rich oxoalkyne) was subjected to benzannulation with phenylacetylene (electron-rich alkyne) under various catalytic systems. Thus, in the presence of 3 mol% of $AuCl_3$ combined with 9 mol% of AgOTf as a catalytic system, the benzannulation product **3f** was isolated in 11% yield (Table 1, entry 2). Interestingly, combination of $AuCl_3$ with $AgSbF_6$ as catalytic ensemble allowed formation of the desired product in 74% yield (entry 3), whereas combination with other silver super halides ($AgBF_4$, $AgPF_6$) proves to be less efficient (entries 4 and 5). Thus, $AuCl_3/AgSbF_6$ catalytic system was found to be the most effective for such reactions (Table 1).[10] Note that silver only catalysis does not give the desired product (entry 6, Table 1); decomposition of the starting oxoalkyne **1a** was the result.

After finding the optimal conditions (Table 1), this methodology was then applied to a series of electronically rich oxoalkynes with alkynes as presented in Table 2. As can be seen from Table 2, like phenylacetylene, 4-methylphenylacetylene (Table 2, entry 2) also participates in the reaction. Interestingly, strong electron donors, for example, OMe or NMe_2 on the aryl ring of phenylacetylene speed up the reaction as would be expected based on FMO considerations (entries 3, 4).[11] Other oxoalkynes, for example, **1d**[9] also reacts with phenylacetylene to afford desired benzannulated product in high yield (entry 5).[12] Looking at all the products from Table 2 [all potential chelate ligands for the gold(III) square planar system], one would have suspected product inhibition of the gold(III)



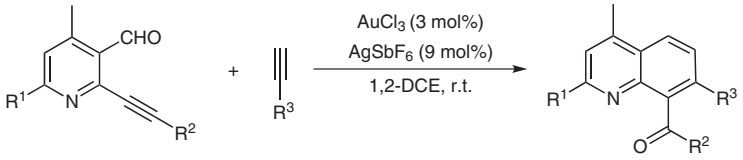
Scheme 2 Possible benzannulation between electron-deficient oxoalkynes with electron-deficient alkynes

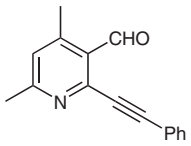
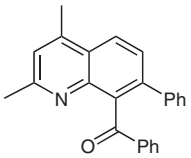
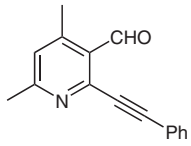
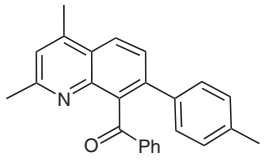
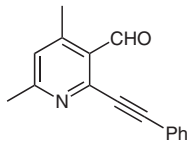
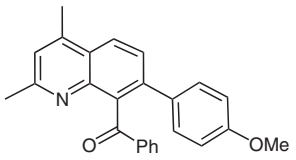
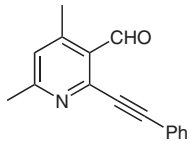
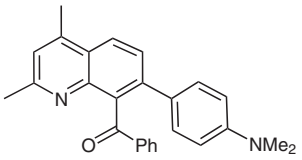
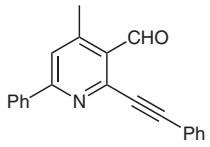
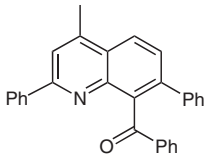
catalyst, which seemingly is not the case.[13] Note that all the reactions in Table 2 were tested using $AuCl_3$ as catalyst and did not give any trace of the desired product.

After successful benzannulation of electron-rich oxoalkynes with electron-rich alkynes, the next challenge was to solve the benzannulation between electron-deficient oxoalkynes with electron-deficient alkynes. In order to facilitate the benzannulation between electron-deficient oxoalkynes with electron-deficient alkynes, either the isobenzopyrylium auric ate complexes or the alkynes must be transformed into electron-rich species. In this context, our idea was to add an alcohol to an electron-deficient alkyne so as to convert the latter into electron-rich enol ether (compared to the starting alkyne). This species may now react with an electron-deficient isobenzopyrylium auric ate complex and subsequent elimination of alcohol (aromaticity-driven) leads to the desired benzannulated product (Scheme 2). This idea though is not without a snag. For example, the liberated alcohol present in the reaction milieu can react with an azaiosobenzopyrylium auric ate complex and may yield the addition product **15** as by-product upon protodeauration (Scheme 3).[14]

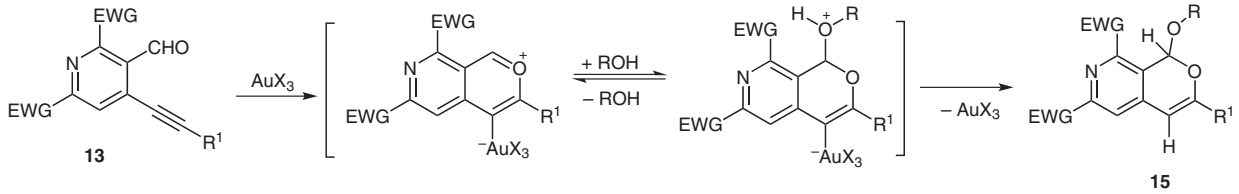
One may consider that addition of alcohol to azaisobenzopyrylium auric ate complexes is reversible, whereas protodeauration is not. Thus, to get away with the undesired alcohol addition reaction it is necessary to prevent the pro-

Table 2 Benzannulation for Rich/Rich Systems[a]



Entry	Oxoalkyne	Time	Product	Yield (%)[b]
1	 **1a**	24 h	 **3f**	74
2	 **1a**	24 h	 **7**	71
3	 **1a**	16 h	 **8**	70
4	 **1a**	12 h	 **9**	61
5	 **1d**	24 h	 **10**	79

[a] All reactions were performed using oxoalkynes (0.2 mmol) and alkynes (0.4 mmol) in the presence of a combination of $AuCl_3$ (3 mol%) and $AgSbF_6$ (9 mol%) in 1,2-dichloroethane (4 mL) at r.t.
[b] Isolated yield.

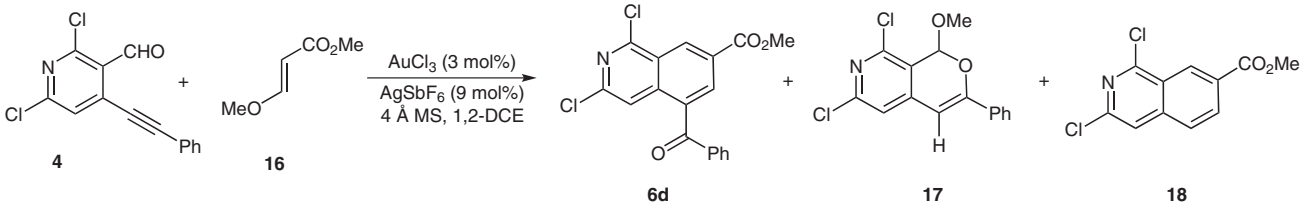


Scheme 3 Possible addition of alcohol to azaisobenzopyrylium auric ate complex

todeauration step in the first place. It is clear that basicity and nucleophilicity of the carbon–gold bond is lower when the gold centre is highly electron-deficient in nature (tight binding). Notably, the azaisobenzopyrylium auric ate complexes generated via coordination of oxoalkynes with highly electron-deficient gold complex have lower LUMO thus reducing the HOMO-LUMO gap between enol ethers and azaisobenzopyrylium auric ate complexes. Therefore, in these cases a highly electron-deficient gold complex should be the catalyst of choice.

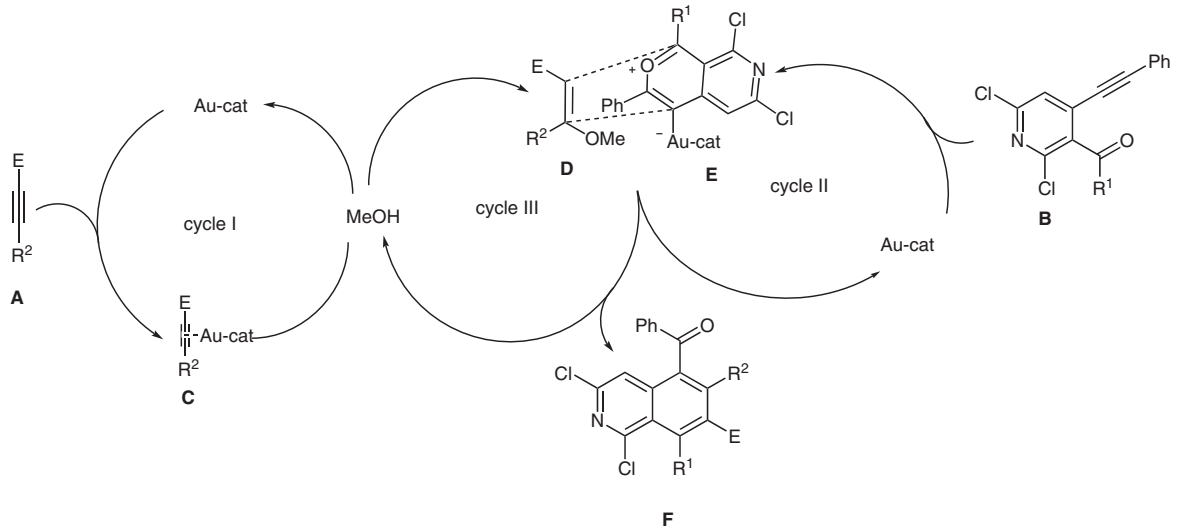
To bring this idea to fruition, enol ethers were prepared from electron-deficient alkynes by addition of alcohols. Thus, reaction of the enol ether **16**[15] with electron-deficient oxoalkyne **4**[16] under $AuCl_3/AgSbF_6$ catalytic condition at room temperature gave 25% of the desired product **6d** along with 46% of methanol addition product **17** (Table 3, entry 1). Gratifyingly, the yield of the desired product **6d** increased to 74% along with 9% debenzoylated product **18** when the reaction temperature was raised to 50 °C. On the other hand, the product ratio was reversed

Table 3 Optimization Study for Benzannulation of an Oxoalkyne with an Enol Ether



Entry	Temp (°C)	Time (h)	Yield (%)[b]		
			6d	**17**	**18**
1	r.t.	24	25	46	0
2	50	12	74	trace	9
3	80	3	23	0	64

[a] All reactions were performed using oxoalkynes (0.2 mmol) and enol ether (0.4 mmol) in the presence of a combination of $AuCl_3$ (3 mol%) and $AgSbF_6$ (9 mol%) in 1,2-dichloroethane (6 mL).
[b] Isolated yield.



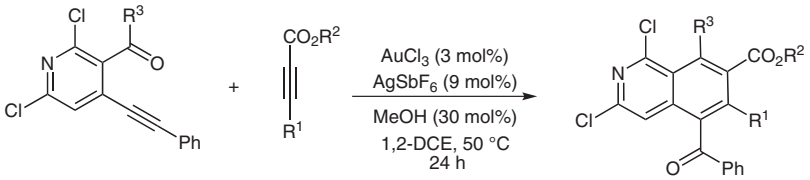
Scheme 4 Plausible mechanism for benzannulation of deficient/deficient systems

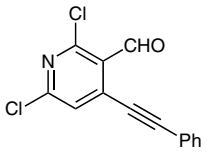
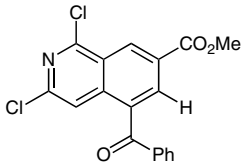
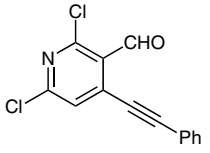
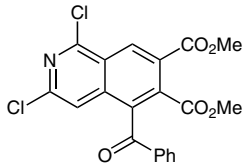
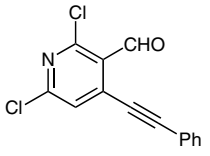
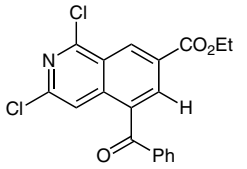
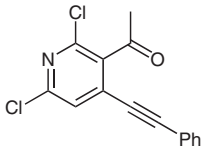
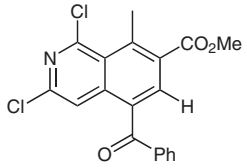
under refluxing conditions: the debenzoylated product **18** was obtained in 64% yield along with 23% of the desired product **6d**.[17]

Our next goal was to perform this reaction in a one-pot tandem and catalytic manner. Reaction of oxoalkyne **4** with methyl propiolate in the presence of catalytic amount of methanol (10%) under gold catalytic conditions furnished 32% of the desired product **6d**. The yield of benzannulation product **6d** was improved to 62% by increasing the amount of alcohol (30 mol%) (Table 4, entry 1). Reaction of **4** with DMAD or ethyl propiolate furnished the desired products **6e** and **19** in moderate yields (Table 4, entries 2, 3). Other oxoalkynes, for example, **20**[16] also reacts with methyl propiolate to afford desired benzannulated product **21** in good yield (entry 4). Note that traces of corresponding methanol addition products were found (TLC) in all the cases reported in Table 4.[18]

A plausible mechanism for the gold-catalyzed[19] formal [4+2] benzannulation (cf. Table 4) of electron-deficient pyridine containing oxoalkynes with electron-deficient alkynes is shown in Scheme 4. The reaction involves three catalytic cycles. In cycle I, the coordination of the triple bond of alkyne **A** to gold catalyst enhances the electrophilicity of the alkyne. Subsequently, the nucleophilic attack of methanol to the electron-deficient alkyne complex **C** followed by protodeauration leads to the formation of the enol ether **D** and regeneration of the gold catalyst. On the other hand, in cycle II, the coordination of the triple bond of oxoalkyne **B** to gold catalyst enhances the electrophilicity of the triple bond. Subsequently, the nucleophilic attack of the carbonyl oxygen to the activated triple bond leads to the formation of the intermediate azaisobenzopyrylium auric ate complex **E**. Now the Diels–Alder type [4+2] cycloaddition of azaisobenzopyrylium auric ate

Table 4 Benzannulation of Deficient/Deficient Systems[a]



Entry	Oxoalkyne	Product	Yield (%)[b]
1	 **4**	 **6d**	62
2	 **4**	 **6e**	56
3	 **4**	 **19**	61
4	 **20**	 **21**	57

[a] All reactions were performed using oxoalkynes (0.4 mmol) and alkynes (0.8 mmol) in the presence of a combination of $AuCl_3$ (3 mol%), $AgSbF_6$ (9 mol%), and MeOH (30 mol%) in 1,2-dichloroethane (8 mL) at 50 °C.
[b] Isolated yield.

complex **E** with an enol ether **D** forms the intermediate cycloadduct and consequent bond rearrangement gives the isoquinoline derivatives **F** and regenerates the gold catalyst and alcohol (cycle III).

In conclusion, we have successfully developed a new and useful procedure for the benzannulation reaction between electron-rich oxoalkynes with electron-rich alkynes using highly electron-deficient gold catalysts. Additionally, using catalytic amount of methanol we have developed an attractive procedure for the benzannulation reaction between electron-deficient oxoalkynes with electron-deficient alkynes.

All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at the 400 MHz and 100 MHz or 200 MHz and 50 MHz in $CDCl_3$ with residual $CHCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.2 ppm) as an internal reference. The data are reported in the following order: chemical shift in ppm (δ); multiplicity (standard abbreviations); coupling constants in *J* (Hz). Analytical TLC was performed on silica gel 60 precoated plates with QF-254 indicator. Visualization was accomplished by UV light, I_2 vapor, or 2,4- dinitrophenylhydrazine solution. Column chromatography was performed on silica gel (230–400 mesh) using EtOAc and petroleum ether (PE, bp 60–80 °C) mixture as eluent. Unless otherwise stated, all reactions were carried out under an argon atmosphere in flame-dried flasks. All reagents were commercially available and, where appropriate, purified prior to use, unless specified otherwise. Solvents were dried as follows: MeCN and 1,2-dichloroethane (1,2-DCE) over P_4O_{10}. After workup, anhyd Na_2SO_4 was used as the drying agent; organic extracts were evaporated under reduced pressure and the residue was purified by column chromatography.

Benzannulation of Both Electron-Rich Oxoalkynes with Alkynes, General Procedure

$AgSbF_6$ (6 mg, 0.018 mmol, 9 mol%) was added to a solution of $AuCl_3$ (2 mg, 0.006 mmol, 3 mol%) in 1,2-dichloroethane (3 mL). After stirring at r.t. for 15 min, a mixture of respective oxoalkyne **1** (0.2 mmol) and respective alkyne (0.4 mmol) in 1,2-dichloroethane (3 mL) was added dropwise and stirring was continued at r.t. for the stated time in Table 2. After completion of the reaction (TLC, eluent: 10% EtOAc–PE), solvent was removed, and the product purified by column chromatography over silica gel (Table 2).

(2,4-Dimethyl-7-phenylquinolin-8-yl)phenylmethanone (3f)

From **1a** (0.050 g); yield: 0.053g (74%); white solid; mp 148–150 °C; R_f = 0.26 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.0 Hz, 1 H), 7.65 (d, *J* = 6.0 Hz, 2 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.42–7.36 (m, 3 H), 7.29–7.21 (m, 5 H), 7.11 (s, 1 H), 2.71 (s, 3 H), 2.48 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.5, 159.6, 146.3, 143.6, 140.2, 139.9, 138.9, 137.6, 132.7, 129.6, 129.5, 128.4, 128.2, 127.7, 127.4, 125.5, 124.6, 123.2, 25.5, 18.8.

HRMS (FAB MS): *m*/*z* (M + H)$^+$ calcd for $C_{24}H_{20}NO$: 338.1545; found: 338.1539.

(2,4-Dimethyl-7-*p*-tolylquinolin-8-yl)phenylmethanone (7)

From **1a** (0.05 g); yield: 0.052 g (71%); white solid; mp 142–144 °C; R_f = 0.30 (10% EtOAc–PE).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 7.6 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 7.41 (t, *J* = 7.4 Hz, 1 H), 7.29–7.25 (m, 4 H), 7.09–7.05 (m, 3 H), 2.70 (s, 3 H), 2.47 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 159.5, 146.4, 143.6, 140.1, 138.9, 137.5, 137.3, 136.9, 132.7, 129.7, 129.4, 129.2, 128.3, 127.5, 125.4, 124.6, 123.0, 25.5, 21.3, 18.8.

HRMS (CI MS): *m*/*z* (M + H)$^+$ calcd for $C_{25}H_{22}NO$: 352.1696; found: 352.1696.

[7-(4-Methoxyphenyl)-2,4-dimethylquinolin-8-yl]phenylmethanone (8)

From **1a** (0.05 g); yield: 0.054 g (70%); white solid; mp 136–138 °C; R_f = 0.24 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 7.2 Hz, 2 H), 7.55 (d, *J* = 8.6 Hz, 1 H), 7.41–7.26 (m, 5 H), 7.08 (s, 1 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 3.75 (s, 3 H), 2.70 (s, 3 H), 2.47 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.5, 159.3, 143.6, 139.8, 138.8, 132.7, 132.3, 130.7, 130.0, 129.6, 128.7, 128.3, 127.5, 125.3, 124.6, 123.5, 123.0, 114.0, 55.4, 25.6, 18.8.

HRMS (CI MS): *m*/*z* (M + H)$^+$ calcd for $C_{25}H_{22}NO_2$: 368.1650; found: 368.1654.

[7-(4-Dimethylaminophenyl)-2,4-dimethylquinolin-8-yl]phenylmethanone (9)

From **1a** (0.05 g); yield: 0.048 g (61%); yellow solid; mp 156–158 °C; R_f = 0.21 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.6 Hz, 1 H), 7.69 (d, *J* = 7.7 Hz, 2 H), 7.58 (d, *J* = 8.6 Hz, 1 H), 7.41–7.23 (m, 5 H), 7.05 (s, 1 H), 6.61 (d, *J* = 8.8 Hz, 2 H), 2.89 (s, 6 H), 2.67 (s, 3 H), 2.45 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.0, 159.2, 150.0, 146.6, 143.5, 140.4, 139.0, 136.6, 132.5, 130.3, 129.6, 128.6, 128.2, 127.6, 124.9, 124.4, 122.6, 112.3, 40.4, 25.4, 18.7.

HRMS (FAB MS): *m*/*z* (M + H)$^+$ calcd for $C_{26}H_{25}N_2O$: 381.1967; found: 381.1964.

(4-Methyl-2,7-diphenylquinolin-8-yl)phenylmethanone (10)

From **1d** (0.06 g); yield: 0.063 g (79%); white solid; mp 136–138 °C; R_f = 0.36 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.6 Hz, 1 H), 7.82–7.74 (m, 5 H), 7.65 (d, *J* = 8.6 Hz, 1 H), 7.48–7.42 (m, 3 H), 7.36–7.28 (m, 8 H), 2.81 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 199.3, 156.4, 146.6, 144.6, 141.0, 139.8, 139.4, 139.0, 138.2, 132.7, 129.6, 129.5, 129.4, 128.7, 128.6, 128.4, 128.3, 127.9, 127.5, 126.2, 124.8, 119.4, 19.3.

HRMS (TOF MS): *m*/*z* (M + H)$^+$ calcd for $C_{29}H_{22}NO$: 400.1701; found: 400.1660.

Benzannulation of Both Electron-Deficient Oxoalkynes with Alkynes; General Procedure

$AgSbF_6$ (12 mg, 0.036 mmol, 9 mol%) was added to a solution of $AuCl_3$ (4 mg, 0.012 mmol, 3 mol%) in 1,2-dichloroethane (5 mL). After stirring at r.t. for 15 min, a mixture of the appropriate alkyne (0.8 mmol) and MeOH (4 mg, 30 mol%) in 1,2-dichloroethane (1 mL) (0.3 mL MeOH mixed with 50 mL 1,2-dichloroethane and used as stock solution) was added dropwise and stirring was continued at r.t. for further 15 min. Then, oxoalkyne **4** or **20** (0. 4 mmol) in 1,2-dichloroethane (2 mL) was added to the reaction mixture and the reaction vessel was placed in a preheated oil bath at 50 °C and stirring was continued for 24 h at that temperature. After completion of the reaction (TLC, eluent: 10% EtOAc–PE), the solvent was removed, and the product purified by column chromatography over silica gel (Table 4).

5-Benzoyl-1,3-dichloroisoquinoline-7-carboxylic Acid Methyl Ester (6d)

From **4** (0.11 g); yield: 0.09 g (62%); white solid; mp 153–155 °C; R_f = 0.26 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 8.43 (s, 1 H), 8.04 (s, 1 H), 7.82 (d, *J* = 8.2 Hz, 2 H), 7.68 (t, *J* = 7.1 Hz, 1 H), 7.52 (t, *J* = 7.5 Hz, 2 H), 4.01 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 195.0, 165.2, 153.0, 147.5, 139.4, 136.9, 135.6, 134.5, 132.8, 132.2, 130.6, 129.1, 129.0, 125.9, 118.2, 53.2.

HRMS (CI MS): *m*/*z* $(M + H)^+$ calcd for $C_{18}H_{12}Cl_2NO_3$: 360.0194; found: 360.0141.

5-Benzoyl-1,3-dichloroisoquinoline-6,7-dicarboxylic Acid Dimethyl Ester (6e)

From **4** (0.11 g); yield: 0.093 g (56%); white solid; mp 162–163 °C; R_f = 0.18 (10% EtOAc–PE).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 7.74 (d, *J* = 7.2 Hz, 2 H), 7.64 (m, 1 H), 7.50–7.46 (m, 3 H), 4.00 (s, 3 H), 3.58 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3, 166.3, 165.4, 152.8, 147.5, 138.0, 137.0, 136.4, 135.0, 134.5, 130.8, 130.0, 129.5, 129.4, 129.2, 125.3, 118.2, 53.5, 53.2.

HRMS (CI MS): *m*/*z* $(M + H)^+$ calcd for $C_{20}H_{14}Cl_2NO_5$: 418.0244; found: 418.0247.

5-Benzoyl-1,3-dichloroisoquinoline-7-carboxylic Acid Ethyl Ester (19)

From **4** (0.11 g); yield: 0.091 g (61%); white solid; mp 159–160 °C; R_f = 0.24 (10% EtOAc–PE).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.21 (s, 1 H), 8.44 (s, 1 H), 8.03 (s, 1 H), 7.84 (d, *J* = 7.4 Hz, 2 H), 7.69 (t, *J* = 7.3 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 4.49 (q, *J* = 14.3, 7.0 Hz, 2 H), 1.45 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 164.5, 152.7, 147.1, 139.1, 136.7, 135.4, 134.2, 132.5, 131.7, 130.4, 129.2, 128.8, 125.6, 117.9, 62.1.

HRMS (CI MS): *m*/*z* $(M + H)^+$ calcd for $C_{19}H_{14}Cl_2NO_3$: 374.0345; found: 374.0349.

5-Benzoyl-1,3-dichloro-8-methylisoquinoline-7-carboxylic Acid Methyl Ester (21)

From **20** (0.116 g); yield: 0.085 g (57%); white solid; mp 146–148 °C; R_f = 0.26 (10% EtOAc–PE).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.97 (s, 1 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.8 Hz, 2 H), 3.94 (s, 3 H), 3.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 168.0, 151.2, 145.6, 142.1, 140.2, 137.1, 134.4, 133.5, 132.5, 132.4, 130.6, 129.1, 127.0, 118.1, 53.1, 22.9.

HRMS (CI MS): *m*/*z* $(M + H)^+$ calcd for $C_{19}H_{14}Cl_2NO_3$: 374.0345; found: 374.0349.

6,8-Dichloro-1-methoxy-3-phenyl-1*H*-pyrano[3,4-*c*]pyridine (17)

Prepared following the experimental conditions reported in Table 3, entry 1. From **4** (0.055 g); yield: 0.028 g (46%); white solid; mp 142–143 °C; R_f = 0.32 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.84–7.79 (m, 2 H), 7.48–7.45 (m, 3 H), 7.06 (s, 1 H), 6.49 (s, 1 H), 6.36 (s, 1 H), 3.70 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.3, 150.6, 150.5, 148.0, 143.3, 133.0, 130.8, 129.0, 125.9, 118.8, 117.6, 97.2, 56.7.

HRMS (CI MS): *m*/*z* $(M)^+$ calcd for $C_{15}H_{11}Cl_2NO_2$: 307.0167; found: 307.0167.

1,3-Dichloroisoquinoline-7-carboxylic Acid Methyl Ester (18)

Prepared following the experimental conditions reported in Table 3, entry 3. From **4** (0.055 g); yield: 0.033 g (64%); white solid; mp 146–148 °C; R_f = 0.42 (10% EtOAc–PE).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.03 (s, 1 H), 8.35 (d, *J* = 8.6 Hz, 1 H), 7.84 (d, *J* = 8.6 Hz, 1 H), 7.72 (s, 1 H), 4.03 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 152.6, 145.7, 141.4, 131.8, 130.5, 129.6, 127.0, 125.4, 119.9, 53.0.

HRMS (CI MS): *m*/*z* $(M + H)^+$ calcd for $C_{11}H_8Cl_2NO_2$: 255.9932; found: 255.9899.

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