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Cobalt Catalyzed Tandem Transformation of 2-Aminobenzonitriles to Quinazolinones using Hydration and Dehydrogenative Coupling Strategy

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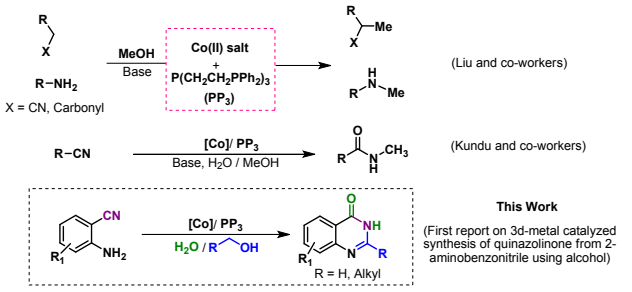
ABSTRACT: A tandem synthesis of quinazolinones from 2-aminobenzonitriles is demonstrated here by using aliphatic alcohol-water system. For this transformation, cheap and easily available cobalt salt and $P(CH_2CH_2PPh_2)_3$ (PP_3) ligand were employed. Substrate scope, scalability and synthesis of natural products exhibited the vitality of this protocol.

INTRODUCTION

Quinazolinones are one of the versatile heterocycles that are found in more than 150 natural alkaloids and pharmaceuticals.[1, 2] Due to the remarkable importance of this skeleton, numerous synthetic methods of these molecules were reported in the literature. However, most of these methods suffer from the usage of expensive or toxic reagents, strong or excess oxidants or multiple-step procedures etc.[3-8] Recently, chemists are more focused on the development of sustainable and economical methods to synthesize fine chemicals and in this context, alcohol is a perfect candidate due to its easy availability from viable resources.[9, 10] In the last few decades, several reports were immersed for the synthesis of quinazolinones by acceptorless dehydrogenative coupling of 2-aminobenzamides and alcohols using various transition metals.[11-16] But in these processes, the use of methanol is very limited due to the high dehydrogenation energy of methanol (ΔH = +84 KJ/mol) compared to other alcohols.[17-20] On the other hand, as methanol is inexpensive and highly abundant molecule, thus utilization of methanol to construct these important molecules is a highly attractive protocol. Amides are easily accessible via hydration of readily available nitriles.[21] Hence, we hypothesized that quinazolinones can be synthesized directly from subsequent hydration 2-aminobenzonitriles and dehydrogenation of methanol in the presence of an efficient catalyst. In literature, few reports are known for the synthesis of quinazolinones from 2-aminobenzonitriles. However, these protocols require either acid/ acid chloride/ aldehydride or stoichiometric amount of aldoxime or precious metal catalysts or they are limited to benzyl alcohols.[22-26] Hence, to synthesize these molecules, development of more effective catalytic system based on non-precious metal is highly desirable.

Development of sustainable processes to synthesize important diverse molecules using cheap and earth-abundant metals is one of the major focuses in current research.[27-31] Recently, a combination of simple cobalt salts with commercially available tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) ligand has become an attractive catalytic system to synthesize various value-added products using alcohol dehydrogenative coupling reactions. In 2017, Liu group independently reported α-methylation of ketones and arylacetonitriles, C3 methylation of indoles and N-methylation of amines using this cobalt system and methanol.[32, 33] Afterward, our group conveyed a tandem transformation of nitrile to N-methylated amide using methanol and water mixture.[34] Inspired by these recent progress herein, we report cobalt catalyzed direct synthesis of quinazolinones from 2-aminobenzonitriles using alcohol-water system (Scheme 1). Recently, we explored this process with expensive ruthenium-based metal complex.[19] However, to the best of our knowledge, it is the first example of 3d metal-catalyzed synthesis of quinazolinone from 2-aminobenzonitriles using alcohol.

Scheme 1. Utilization of [Co]/ PP_3 System in Alcohol Dehydrogenative Coupling Reactions

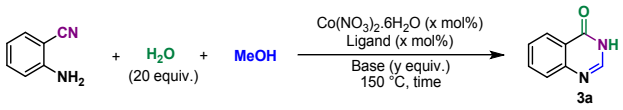


RESULTS AND DISCUSSION

To optimize this tandem synthesis of quinazolinone, 2-aminobenzonitrile was selected as the benchmark substrate. At first, 2-aminobenzonitrile was heated with $CoBr_2$/ tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) system at 150 °C in the presence of 20 equiv. of water in methanol, which afforded 78% yield of the desired quinazolin-4(3H)-one (**3a**) after 24 hours (Table 1, entry 1). Next, keeping other conditions same, different cobalt salts were screened (SI, Table S1, entries 2-6) and among them, cobalt nitrate hexahydrate furnished 98% yield of quinazolin-4(3H)-one (Table 1, entry 2). Furthermore, 80% yield of **3a** was obtained from the same reaction in lower time (16 h) (Table 1, entry 3). Next, different bidentate and tridentate nitrogen and phosphine based ligands (**L_2-L_6**) were

examined (Table 1, entries 4-8). However, they performed poorly in this reaction. After screening cobalt salts and ligands, the effect of different bases was vetted (SI, Table S1, entries 14-21). Among the various bases, Cs_2CO_3 displayed the superior activity in this reaction. Notably, in the presence of air, a lower yield of **3a** was observed (Table 1, entry 9). Next, the catalyst loading was decreased, and the reaction time was increased (Table 1, entries 10-11), and it was observed that 7.5 mol% of cobalt nitrate hexahydrate with PP_3 was sufficient to afford more than 85% yield of the desired product after 24 hours (Table 1, entry 10). Subsequently, the amount of Cs_2CO_3 was reduced to 1.5 equiv., which furnished

Table 1. Optimization Data for Synthesis of Quinazolinones using 2-Aminobenzonitrile and Methanol[a]



Entry	Ligand (mol%)	Base (equiv.)	Time	Yield %
1[b]	PP_3 (10%)	Cs_2CO_3 (2)	24	78
2	PP_3 (10%)	Cs_2CO_3 (2)	24	98
3	PP_3 (10%)	Cs_2CO_3 (2)	16	80
4	L_2 (10%)	Cs_2CO_3 (2)	16	ND
5	L_3 (10%)	Cs_2CO_3 (2)	16	ND
6	L_4 (10%)	Cs_2CO_3 (2)	16	ND
7	L_5 (10%)	Cs_2CO_3 (2)	16	ND
8	L_6 (10%)	Cs_2CO_3 (2)	16	<10
9[c]	PP_3 (10%)	Cs_2CO_3 (2)	16	35
10	PP_3 (7.5%)	Cs_2CO_3 (2)	24	87
11	PP_3 (5%)	Cs_2CO_3 (2)	24	60
12	PP_3 (7.5%)	Cs_2CO_3 (1.5)	24	81
13	PP_3 (7.5%)	Cs_2CO_3 (1)	24	63
14[d]	PP_3 (7.5%)	Cs_2CO_3 (1.5)	24	74
15[e]	PP_3 (7.5%)	Cs_2CO_3 (1.5)	24	65
15[f]	PP_3 (7.5%)	Cs_2CO_3 (1.5)	24	56

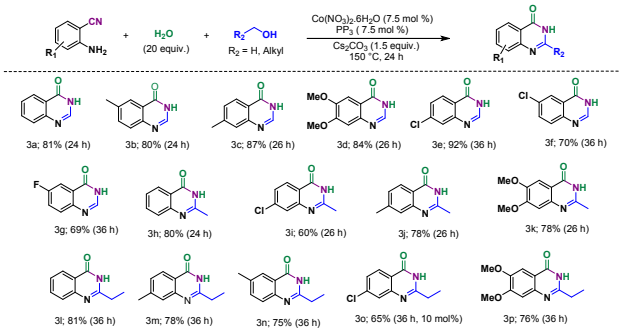
[a]Reaction Conditions: 2-Aminobenzonitrile (0.5 mmol), $Co(NO_3)_2.6H_2O$ (x mol%), ligand (x mol%), base (y equiv.), water (20 equiv.) and methanol (3.6 mL) at 150 °C (oil bath temperature) for specified time under argon atmosphere. [b]$CoBr_2$ (10 mol%). [c]under air. [d]water (10 equiv.). [e]water (40 equiv.). [f]140 °C (oil bath temperature).

81% yield of quinazolinone (Table 1, entry 12). However, the yield of quinazolinone was significantly diminished with further reduction of the amount of Cs_2CO_3 (SI, Table S1, entry 25). In this reaction, the amount of water played a vital role, 20 equiv. of water provided the best yield (Table 1, entries 14-15). The combination of methanol with other solvents and lower reaction temperature did not work well with this system (SI, Table S1, entries 28-31).

After optimization of the reaction conditions, the scope of this protocol was explored with a variety of 2-aminobenzonitriles and methanol. In the standard reaction conditions, various substituted 2-aminobenzonitriles having both electron-donating groups such as -Me, -OMe, and electron-withdrawing groups like –Cl and –F at different positions, afforded the desired products in good to moderate yields (Scheme 2, **3a-g**). Similarly, ethanol and 1-propanol also effectively coupled with the variety of 2-aminobenzonitriles (Scheme 2, **3h-p**). Notably, with these three alcohols, this tandem reaction was relatively slower in the case of electron-deficient 2-aminobenzonitriles compared to 2-aminobenzonitriles having electron-donating groups.

However, with 1-butanol and other long-chain primary alcohols surprisingly lower yields of the desired products were observed (SI, Table S2, entries 1-3). We hypothesized that probably the formation of the desired PP_3 bound cobalt complex was not smooth in these higher aliphatic alcohols. The

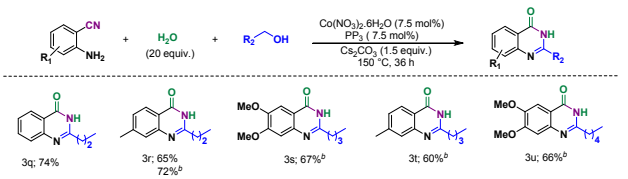
Scheme 2. Synthesis of Quinazolinone Derivatives using 2-Aminobenzonitriles and Aliphatic Alcohols[a]



[a]Reaction Conditions: 2-Aminobenzonitrile (0.5 mmol), $Co(NO_3)_2.6H_2O$ (7.5 mol%), PP_3 (7.5 mol%), Cs_2CO_3 (1.5 equiv.), water (20 equiv.) and methanol (3.6 mL) at 150 °C (oil bath temperature) for specified time under argon atmosphere.

possible reason could be the lower polarity of long-chain alcohols compared to the smaller alcohols. Hence, the reaction procedure for higher aliphatic alcohols was modified. First, the cobalt salt and ligand were stirred at room temperature for 30 minutes in the alcohol and subsequently, 2-aminobenzonitriles and other reagents were added to the mixture and the overall mixture was heated for the specified time. Following this protocol, the yield of the desired quinazolinone was increased

Scheme 3. Synthesis of Quinazolinone Derivatives from 2-Aminobenzonitriles and Long Chain Primary Alcohols[a]



[a]Reaction Conditions: $Co(NO_3)_2.6H_2O$ (7.5 mol%), PP_3 (7.5 mol%) and alcohol (3.6 mL) were stirred at room temperature for 30 minutes followed by addition of 2-aminobenzonitrile (0.5 mmol), Cs_2CO_3 (1.5 equiv.), water (20 equiv.); heated at 150 °C

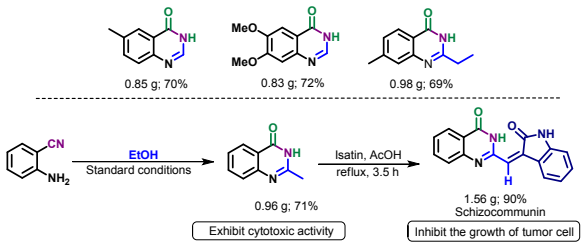
(oil bath temperature) for 36 h under argon atmosphere. [b] $Co(NO_3)_2.6H_2O/PP_3$ (10 mol%).

significantly with 1-butanol (SI, Table S2, entry 5). Other conditions such as the combination of different solvents and different stirring time at room temperature were also tested (SI, Table S2) but all the cases lower amount of yield was observed. Next, following this modified protocol, a variety of quinazolinones were successfully synthesized from different 2-aminobenzonitriles and higher chain aliphatic alcohols in good to moderate yields (Scheme 3, **3q-u**).

Next, the synthetic applicability of this methodology was examined by the gram-scale synthesis of various quinazolinones (Scheme 4). Additionally, biologically active schizocommunin was synthesized in a preparative scale applying this methodology (Scheme 4).[35] Initially, 2-methylquinazolin-4(3H)-one (**3h**) was synthesized from 2-aminobenzonitrile and ethanol. Afterward, schizocommunin was prepared in good yield by coupling **3h** and isatin in acetic acid medium.

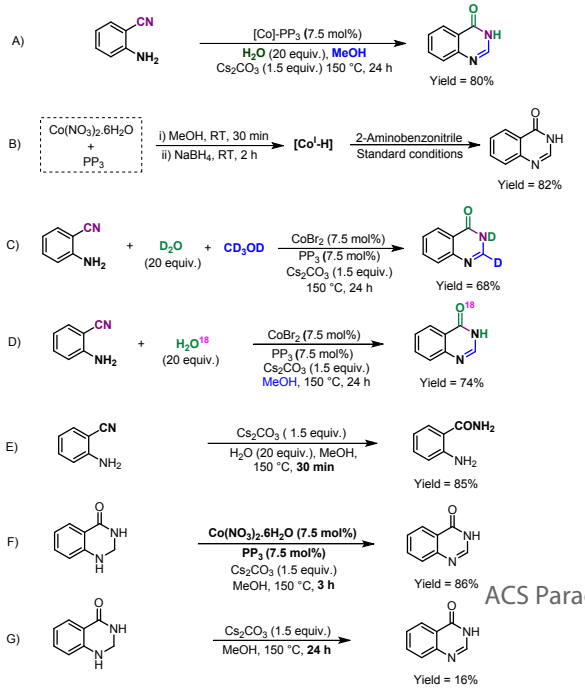
After successful implementation of the protocol to synthesize various quinazolinone derivatives from 2-aminobenzinitriles, different control and kinetic experiments were performed to understand the mechanism for this tandem

Scheme 4. Synthesis of Quinazolinones in Preparative Scale



transformation. Instead of using cobalt salt and ligand separately, isolated cobalt complex was synthesized by the stirring of $Co(NO_3)_2.6H_2O$ and PP_3 in methanol, which produced a similar yield of quinazolin-4(3H)-one (Scheme 5A). Next, following the literature procedure, $[(PP_3)Co^{I}\text{-}H]$ was separately synthesized, which afforded 82% yield of the desired product under the standard reaction conditions (Scheme 5B).[36, 37] This result indicated the involvement of $[(PP_3)Co^{I}\text{-}H]$ species

Scheme 5. Mechanistic Investigation

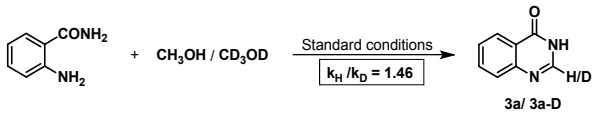


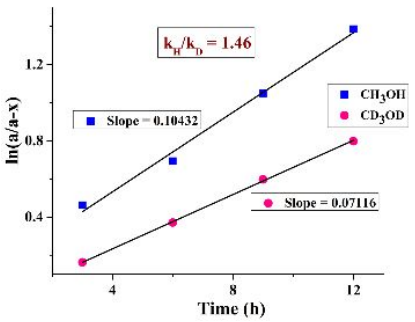
in this reaction. Afterward, upon performing the reaction of 2-aminobenzonitrile with isotope labeled methanol (CD_3OD) and water (D_2O), the di-deuterium incorporated product was formed (Scheme 5C). This experiment confirmed that methanol was the source of the C-2 carbon of quinazolinone. O^{18}-incorporated quinazolin-4(3H)-one was formed when the standard reaction was performed in the presence of H_2O^{18} which confirmed that water was the source of the oxygen atom in the desired product (Scheme 5D). It is worth to mention that the above two experiments were carried out using anhydrous $CoBr_2$ in the place of $Co(NO_3)_2.6H_2O$ to avoid isotopic scrambling.

Next, under the reaction conditions in the absence of cobalt salt and ligand, 2-aminobenzonitrile was converted 2-aminobenzamide in 85% yield within 30 minutes (Scheme 5E). This outcome indicated that the nitrile hydration step was quite faster. 2,3-Dihydroquinazolinone is considered as one of the intermediates in this process. Hence, this molecule was separately synthesized, and the dehydrogenation of this compound under the standard reaction conditions was investigated. Dehydrogenation of 2,3-dihydroquinolin-4(1H)-one was much faster in the presence of the cobalt catalyst; 86% yield of the desired quinolin-4(3H)-one was obtained after 3 hours (Scheme 5F), whereas only 16% yield of desired product was observed after 24 hours in the absence of the cobalt catalyst (Scheme 5G).

This tandem reaction of 2-aminobenzamide using CH_3OH and CD_3OD disclosed a k_H/k_D of 1.46 (Scheme 6). This moderate KIE value indicated that dehydrogenation of methanol might not be the most energy demanding step in this protocol.[19] However, at this moment, it is very difficult to identify which step might be the rate-determining step in this multi-step tandem transformation, and for this purpose, DFT calculations are currently going on in our laboratory.

Scheme 6. Kinetic Isotope Effect (KIE) Experiment for Synthesis of 3a from 2-Aminobenzamide

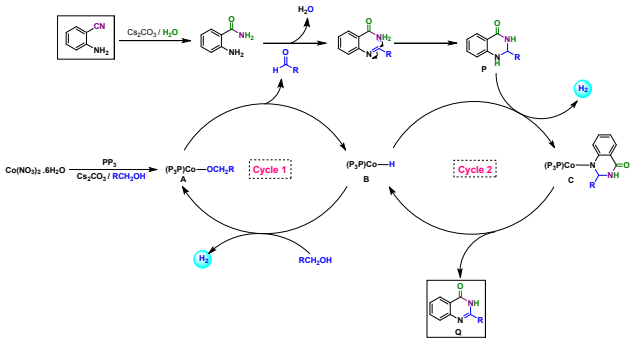




Based on mechanistic studies and previous reports, a plausible catalytic cycle was proposed (Scheme 7).[32] In cycle 1, in the presence of base and alcohol, alkoxy bound cobalt species **A** would form, which would further undergo β-H elimination to form corresponding aldehyde and [Co]-H

species **B**. Afterwards, the aldehyde would couple with 2-aminobenzamide which was generated *in-situ* from hydration of 2-aminobenzonitrile and subsequently via cyclization would produce 2,3-dihydroquinazolinone **P**. Next, in cycle 2, in the presence of 2,3-dihydroquinazolinone **P** and previously formed [Co]-H species, **B** would transform to species **C** and hydrogen was liberated. Later, the dehydrogenation of species **C** would produce the desired quinazolinone **Q** and would regenerate the [Co]-H species. Afterward, in cycle 1, with the help of another molecule of alcohol, [Co]-H species would convert back to alkoxy-bound cobalt species **A** and one molecule hydrogen would release.

Scheme 7. Plausible Reaction Mechanism



In summary, cobalt catalyzed an effective and sustainable protocol was developed for the tandem synthesis of quinolin-4(3H)-ones from 2-aminobenzonitriles. Following this methodology, several quinazolinone derivatives were synthesized from different short and long chain aliphatic alcohols. To extend the practical applicability of this protocol, biologically active natural product schizocommunin and few quinazolinones were synthesized in the preparative scale. Several control experiments and kinetic studies were also performed to understand this tandem process. To the best of our knowledge, this is the first 3d metal-based catalytic system for the tandem synthesis of different quinolin-4(3H)-one derivatives from various 2-aminobenzonitriles using aliphatic alcohols and water.

EXPERIMENTAL SECTION

1. General procedures and materials: All the experiments were carried out under inert atmosphere using either standard Schlenk line techniques or argon filled Glove box. Glass apparatus were oven-dried overnight at 100 °C before use. Solvents were dried according to standard literature methods and deoxygenated with inert gas prior to use. All 2-aminobenzonitriles derivatives, cobalt precursors and other commercially available reagents were purchased from Sigma-Aldrich, Alfa-Aesar, TCI-India, SDFCL, Avra and Spectrochem. ^{1}H and ^{13}C spectra were recorded on JEOL 400 and 500 MHz spectrometers. All ^{1}H and proton decoupled ^{13}C NMR spectra were reported in ppm relative to residual DMSO peak (2.5 ppm) and deuterated DMSO (39.5 ppm) respectively. ESI-MS were recorded on a Waters Micromass Quattro Micro triple-quadrupole mass spectrometer and Bruker's Maxis Impact (282001.00081). Elemental analysis was carried out on a Thermoquest EA1110 CHNS/O analyzer.

2. General synthesis procedures

2A. Coupling of 2-aminobenzonitriles with short chain alcohol (methanol, ethanol, 1-propanol): In a pressure tube, magnetic stir-bar, 2-aminobenzonitrile derivatives (0.5 mmol), $Co(NO_3)_2.6H_2O$ (7.5 mol%), tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) (7.5 mol%), Cs_2CO_3 (1.5 equiv.), water (20 equiv.) and alcohol (methanol, ethanol and 1-propanol) (3.6 mL) were added under argon atmosphere. Then, the tube was sealed and dipped in a preheated oil-bath at 150 °C for specified time. After completion of the reaction, the tube was allowed to cool to room temperature and the reaction mixture was concentrated under reduced pressure. Finally, the desired product was purified through silica gel column chromatography using hexane/ethyl acetate as the eluent. The polarity of eluent was increased gradually from 30% (ethyl acetate/hexane, v/v = 3:7) to 60% (ethyl acetate/hexane, v/v = 6:4) to purify the desired products.

2B. Coupling of 2-aminobenzonitriles with other long chain alcohols (1-butanol, 1-pentanol and 1-hexanol): In a pressure tube, magnetic stir-bar, $Co(NO_3)_2.6H_2O$ (7.5-10 mol%) and tris[2-(diphenylphosphino)ethyl]phosphine (PP_3) (7.5-10 mol%) were stirred in the long chain alcohol (1-butanol, 1-pentanol and 1-hexanol) (3.6 mL) for 30 minutes at room temperature under argon atmosphere and subsequently, 2-aminobenzonitrile derivatives (0.5 mmol), Cs_2CO_3 (1.5 equiv.), water (20 equiv.) were added to the mixture. The overall mixture was subjected to heating for specified reaction time. After completion of the reaction, the tube was allowed to cool to room temperature and the reaction mixture was concentrated under reduced pressure. Finally, the desired product was purified through silica gel column chromatography using hexane/ethyl acetate as the eluent. The polarity of eluent was increased gradually from 30% (ethyl acetate/hexane, v/v = 3:7) to 60% (ethyl acetate/hexane, v/v = 6:4) to purify the desired products.

Quinazolin-4(3H)-one (3a)[18]: This product was synthesized following the general procedure 2A by reacting 2-aminobenzonitrile (59 mg, 0.5 mmol) and methanol (3.6 mL). The title product was a white solid (59 mg, 81% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.24 (brs, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H), 7.79 (t, J = 7.1 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 7.51 (t, *J* = 8 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d6): δ = 160.8, 148.8, 145.5, 134.3, 127.3, 126.8, 125.9, 122.7.

6-Methylquinazolin-4(3H)-one (3b)[18]: This product was synthesized following the general procedure 2A by reacting 2-amino-5-methylbenzonitrile (66 mg, 0.5 mmol) and methanol (3.6 mL). The title product was a light yellow solid (64 mg, 80% isolated yield). For 1g scale reaction isolated yield was 70% (0.85 g). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.02 (s, 1H), 7.90 (s, 1H), 7.62 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 2.43 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 163.1, 160.9, 146.8, 144.9, 136.4, 127.0, 125.2, 122.4, 20.8.

7-Methylquinazolin-4(3H)-one (3c)[18]: This product was synthesized following the general procedure 2A by reacting 2-amino-4-methylbenzonitrile (66 mg, 0.5 mmol) and methanol (3.6 mL). The title product was a white solid (69 mg, 87% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.14 (brs, 1H), 8.05 (s, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.46 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 2.44 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 160.6, 148.9, 145.4, 144.8, 128.2, 126.9, 125.7, 120.2, 21.3.

6,7-Dimethoxyquinazolin-4(3H)-one (3d)[18]: This product was synthesized following the general procedure 2A by reacting 2-amino-4,5-dimethoxybenzonitrile (89 mg, 0.5 mmol) and methanol (3.6 mL). The title product was a grey solid (86 mg, 84% isolated). For the 1g scale reaction isolated yield was 72% (0.83 g). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.06 (brs, 1H), 7.98 (s, 1H), 7.43 (s, 1H), 7.12 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 160.0, 154.4, 148.5, 144.9, 143.8, 115.6, 108.0, 104.9, 55.9, 55.7.

7-Chloroquinazolin-4(3H)-one (3e)[18]: This product was synthesized following the general procedure 2A by reacting 2-amino-4-chlorobenzonitrile (76 mg, 0.5 mmol) and methanol (3.6 mL). The title product was a white solid (83 mg, 92% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.11 (s, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.52 (dd, *J* = 8.6, 2.0 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 160.3, 149.9, 147.0, 139.0, 128.0, 127.1, 126.4, 121.5.

6-Chloroquinazolin-4(3H)-one (3f)[18]: This product was synthesized following the general procedure 2A by reacting 2-amino-5-chlorobenzonitrile (76 mg, 0.5 mmol) and methanol (3.6 mL). The title product was a white solid (63 mg, 70% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.44 (brs, 1H), 8.12 (s, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 159.8, 147.5, 145.9, 134.4, 131.0, 129.5, 124.8, 123.9.

6-Fluoroquinazolin-4(3H)-one (3g)[18]: This product was synthesized following the general procedure 2A by reacting 2-amino-5-fluorobenzonitrile (68 mg, 0.5 mmol) and methanol (3.6 mL). The title product was a white solid (56 mg, 69% isolated yield). **^{1}H NMR** (500 MHz, DMSO-d_6): δ = 12.31 (brs, 1H), 8.06 (s, 1H), 7.73 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.71-7.68 (m, 1H), 7.64 (td, *J* = 8.6, 3 Hz, 1H). **^{13}C{^{1}H} NMR** (125 MHz, DMSO-d_6): δ = 161.0, 160.2, 159.1, 145.2 (d, *J* = 93.7 Hz), 130.0 (d, *J* = 8.2 Hz), 123.9 (d, *J* = 8.2 Hz), 122.7 (d, *J* = 23.9 Hz), 110.5 (d, *J* = 23.1 Hz).

2-Methylquinazolin-4(3H)-one (3h)[18]**:** This product was synthesized following the general procedure 2A by reacting 2-aminobenzonitrile (59 mg, 0.5 mmol) and ethanol (3.6 mL). The title product was white a solid (64 mg, 80% isolated yield). For 1g scale reaction isolated yield was 71% (0.96 g). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.18 (brs, 1H), 8.05 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.74-7.70 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.8, 154.3, 149.0, 134.2, 126.6, 125.8, 125.7, 120.7, 21.5.

7-Chloro-2-methylquinazolin-4(3H)-one (3i)[38]: This product was synthesized following the general procedure 2A by reacting 2-amino-4-chlorobenzonitrile (76 mg, 0.5 mmol) and ethanol (3.6 mL). The title product was a white solid (58 mg, 60% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.33 (brs, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.8 Hz, 1H), 2.34 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.1, 156.1, 150.1, 138.9, 127.8, 126.2, 125.7, 119.5, 21.5.

2,7-Dimethylquinazolin-4(3H)-one (3j)[39]: This product was synthesized following the general procedure 2A by reacting 2-amino-4-methylbenzonitrile (66 mg, 0.5 mmol) and ethanol (3.6 mL). The title product was a white solid (68 mg, 78% isolated yield); **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.08 (brs, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.36 (s, 1H), 7.26 (d, *J* = 8.1 Hz 1H), 2.42 (s, 3H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.6, 154.3, 149.1, 144.7, 127.3, 126.2, 125.5, 118.2, 21.4, 21.4.

6,7-Dimethoxy-2-methylquinazolin-4(3H)-one (3k)[38]: This product was synthesized following the general procedure 2A by reacting 2-amino-4,5-dimethoxybenzonitrile (89 mg, 0.5 mmol) (59 mg, 0.5 mmol) and ethanol (3.6 mL). The title product was a white solid (86 mg, 78% isolated yield). **^{1}H NMR** (500 MHz, DMSO-d_6): δ = 12.02 (brs, 1H), 7.38 (s, 1H), 7.04 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.30 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.1, 154.5, 152.5, 147.9, 145.1, 113.4, 107.5, 104.8, 55.8, 55.6, 21.2.

2-Ethylquinazolin-4(3H)-one (3l)[18]: This product was synthesized following the general procedure 2A by reacting 2-aminobenzonitrile (59 mg, 0.5 mmol) and 1-propanol (3.6 mL). The title product was a white solid (70 mg, 81% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.14 (brs, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.74 (t, *J* =7.4 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 2.60 (q, *J* =7.36 Hz, 2H), 1.23 (t, *J* =7.88 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.9, 158.4, 149.0, 134.3, 126.8, 126.0, 125.8, 120.9, 27.9, 11.4.

2-Ethyl-7-methylquinazolin-4(3H)-one (3m)[14]: This product was synthesized following the general procedure 2A by reacting 2-amino-4-methylbenzonitrile (66 mg, 0.5 mmol) and 1-propanol (3.6 mL). The title product was a white solid (73 mg, 78% isolated yield). For 1g scale reaction isolated yield was 69% (0.98 g). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.04 (brs, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.38 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 2.59 (q, *J* = 7.4 Hz, 2H), 2.41 (s, 3H) 1.22 (t, *J* = 7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.9, 158.5, 149.1, 144.8, 127.5, 126.5, 125.7, 118.5, 27.9, 21.4, 11.4.

2-Ethyl-6-methylquinazolin-4(3H)-one (3n)[14]: This product was synthesized following the general procedure 2A by reacting 2-amino-5-methylbenzonitrile (66 mg, 0.5 mmol) and 1-propanol (3.6 mL). The title product was a white solid (70 mg, 75% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.04 (brs, 1H), 7.85 (s,1H), 7.56 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 2.40 (s, 3H) 1.22 (t, *J* = 7.6 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.8, 157.4, 147.0, 135.5, 135.4, 126.7, 125.1, 120.6, 27.8, 20.7, 11.3.

7-Chloro-2-ethylquinazolin-4(3H)-one (3o)[14]: This product was synthesized following the general procedure 2A by reacting 2-amino-4-chlorobenzonitrile (76 mg, 0.5 mmol) and 1-propanol (3.6 mL). The title product was a white solid (67 mg, 65% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.29 (brs, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.0 Hz, 1H), 2.61 (q, *J* =7.60 Hz, 2H),1.23 (t, *J* =7.4 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.2, 160.1, 150.1, 138.9, 127.8, 126.2, 125.9, 119.6, 27.9, 11.2.

2-Ethyl-6,7-dimethoxyquinazolin-4(3H)-one (3p)[14]: This product was synthesized following the general procedure 2A by reacting 2-amino-4,5-dimethoxybenzonitrile (89 mg, 0.5 mmol) and 1-propanol (3.6 mL). The title product was a white solid (89 mg, 76% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 11.99 (brs, 1H), 7.40 (s, 1H), 7.07 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.58 (q, *J* =7.6 Hz, 2H),1.22 (t, *J* =7.5 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ =

161.2, 156.7, 154.5, 148.0, 145.1, 113.6, 107.7,104.9, 55.9, 55.6, 27.7, 11.4.

2-Propylquinazolin-4(3H)-one (3q)[40]: This product was synthesized following the general procedure 2B by reacting 2-aminobenzonitrile (59 mg, 0.5 mmol) and 1-butanol (3.6 mL). The title product was a white solid (69 mg, 74% isolated yield. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.15 (brs, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* =7.2 Hz, 1H), 7.58 (d, *J* = 7.1 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 2.56 (t, *J* =7.4 Hz, 2H), 1.78-1.69 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.8, 157.3, 148.9, 134.2, 126.8, 125.9, 125.7, 120.8, 36.3, 20.2, 13.5.

7-Methyl-2-propylquinazolin-4(3H)-one (3r)[41]: This product was synthesized following the general procedure 2B by reacting 2-amino-4-methylbenzonitrile (66 mg, 0.5 mmol) and 1-butanol (3.6 mL). The title product was a white solid (73 mg, 72% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.05 (brs, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.39 (s, 1H), 7.26 (d, *J* = 8.2, Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.77-1.68 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.7, 157.3, 149.1, 144.7, 127.3, 126.5, 125.5, 118.4, 36.3, 21.3, 20.2, 13.5.

2-Butyl-6,7-dimethoxyquinazolin-4(3H)-one (3s): This product was synthesized following the general procedure 2B by reacting 2-amino-4,5-dimethoxybenzonitrile (89 mg, 0.5 mmol) and 1-pentanol (3.6 mL). The title product was a white solid (88 mg, 67% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 11.98 (brs, 1H), 7.39 (s, 1H), 7.05 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.55 (t, *J* = 7.8 Hz, 3H), 1.71-1.64 (m, 2H), 1.37-1.27 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.3, 155.9, 154.5, 148.0, 145.1, 113.78, 107.7, 104.9, 55.9, 55.7, 34.0, 29.0, 21.7, 13.7. LR-MS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{19}N_2O_3$ 263.14; Found 263.16. **Elemental Analysis:** Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.45; H, 6.81; N, 10.43.

2-Butyl-7-methylquinazolin-4(3H)-one (3t): This product was synthesized following the general procedure 2B by reacting 2-amino-4-methylbenzonitrile (66 mg, 0.5 mmol) and 1-pentanol (3.6 mL). The title product was a white solid (65 mg, 60% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.04 (brs, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.24 (d, *J* = 8 Hz, 1H), 2.56 (t, *J* = 7.8 Hz, 2H), 2.41 (s, 3H), 1.69-1.64 (m, 2H), 1.35-1.29 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.8, 157.5, 149.1, 144.7, 127.3, 126.5, 125.5, 118.4, 34.2, 28.9, 21.7, 21.3, 13.7. LR-MS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_{17}N_2O$ 217.13, Found 217.17. **Elemental Analysis**: Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.41; H, 7.23; N, 12.69.

6,7-Dimethoxy-2-pentylquinazolin-4(3H)-one (3u)[19]: This product was synthesized following the general procedure 2B by reacting 2-amino-4,5-dimethoxybenzonitrile (89 mg, 0.5 mmol) and 1-hexanol (3.6 mL). The title product was a white solid (91 mg, 66% isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.00 (brs, 1H), 7.39 (s, 1H), 7.07 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.74-1.66 (m, 2H), 1.33-1.26 (m, 4H), 0.87 (t, *J* = 6.5 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 161.2, 155.9, 154.5, 148.0, 145.1, 113.6, 107.7, 104.8, 55.7, 55.6, 34.3, 30.7, 26.5, 21.8, 13.8.

Schizocommunin[35]: In a Schlenk flask magnetic stir-bar, 2-methyl-4(3H)-quinazolinone (0.96 g, 1.0 mmol) and isatin (0.88 g, 1.0 mmol) were added, and overall mixture was refluxed in glacial acetic acid (6 mL) for 4 h. After that, reaction mixture was allowed to cool to room temperature and the precipitate was filtered. After that, precipitate was washed several times with methanol and dried to get final product schizocommunin as an orange powder (1.56 g, 90% isolated yield).**^{1}H NMR** (400 MHz, DMSO-d_6): δ = 14.39 (s, 1H), 11.48 (brs, 1H), 8.17 (dd, *J* = 6.4, 0.7 Hz, 1H), 7.93 (d, *J* = 6 Hz, 1H), 7.90-7.86 (m, 1H), 7.78 (d, *J* = 6.4 Hz, 1H), 7.60 (t, *J* = 6.2 Hz, 1H), 7.56 (s, 1H), 7.36 (t, *J* = 6.1 Hz, 1H), 7.08 (t, *J* = 6 Hz, 1H), 6.92 (d, *J* = 6.2 Hz, 1H). HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{12}N_3O_2$ 290.0930; Found 290.0923.

mono-deuterium incorporated product (3a-D)[19] This product was isolated during kinetic isotope effect (KIE) experiment by reacting 2-aminobenzamide (68.1 mg, 0.5 mmol) and methanol-d_4 (3.6 mL) for 12 h (see SI). The title product was a white solid (40.5 mg, 55% isolated yield): **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 12.24 (brs, 1H), 8.13-8.09 (m, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.53-7.50 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6): δ = 160.8, 148.8, 134.3, 127.2, 126.7, 126.6, 125.9, 122.7.

ASSOCIATED CONTENT

Detail reaction optimization, preparative scale reaction, control experiments, reaction kinetics and mechanism, preparation of isolated Co (II) complexes, ^{1}H and ^{13}C spectra of all compounds.

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Notes

The authors declare no competing financial interest.

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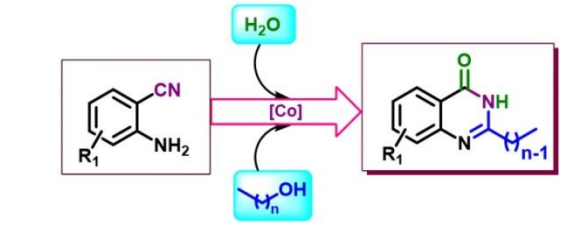

- 1st report with 3d metal
- Commercially available cobalt salt and ligand
- Tandem protocol
- Alcohol dehydrogenative coupling