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Cobalt-Catalyzed *ortho*-C–H Functionalization/Alkyne Annulation of Benzylamine Derivatives: Access to Dihydroisoquinolines

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Abstract: A practical picolinamide-directed C–H functionalization/alkyne annulation of benzylamine derivatives enabling the access to the previously elusive 1,4-dihydroisoquinoline skeleton was developed using molecular O₂ as the sole oxidant and Co(OAc)₂ as precatalyst. The method is compatible with both internal and terminal alkynes and shows high versatility and functional-group tolerance. Furthermore, full preservation of enantiopurity is observed when using non-racemic α -substituted benzylamine derivatives. Kinetic analysis of the reagents and catalyst, labeling experiments and the isolation and identification of catalytically competent Co-complexes revealed important insights about the mechanism.

Introduction

Alkyne annulation of nitrogen containing arenes through C–H/N–H functionalization, in which vicinal C–N and C–C bonds across an alkyne are installed in a single transformation, has proven to be a powerful tactic for the step-economical assembly of various heterocycles with activities of relevance to medicinal chemistry and biology.^[1,2] While impressive progress has been made using second and third row transition metals such as Pd, Rh or Ru,^[2] homogeneous cobalt catalysis is currently drawing much attention as a more abundant, less toxic and cheaper viable alternative.^[3] This increasing demand to move toward more environmentally benign approaches makes also highly desirable to replace the stoichiometric oxidants generally required to maintain the catalytic cycle (most often silver or copper salts) with molecular oxygen, in which no wastes are formed except for water.^[4] However, yet despite the significant progress in this field, reports relying on oxygen as the terminal oxidant remain limited, particularly in the context of cobalt-catalyzed heterocycle synthesis via arene C–H annulation with π -systems. In particular, the first broadly applicable Co-catalyzed aerobic alkyne annulations have appeared only recently.^[5,6] Consequently, catalyst systems combining simple cobalt salts and O₂ as the sole oxidant are being actively sought.

C–H functionalization in concert with alkyne annulation is typically enabled by a bidentate chelating auxiliary,^[7] which is attached to the arene system by a carbonyl or a heteroatom linkage, most often benzamide and related functionalities.^[8] In contrast, to the best of our knowledge, there are only a handful of procedures for the use of benzylamine derivatives in Co-mediated alkyne annulation. Within a general protocol for cobalt-catalyzed, aminoquinoline-directed C(sp²)–H annulation of benzamide derivatives with alkynes, Daugulis disclosed a single isolated example of annulation of a α -methyl-substituted benzylamine-derived picolinamide substrate with 2-butyne in the presence of a stoichiometric amount of cobalt in combination with 2 equiv of Mn(OAc)₂ as cooxidant and O₂ (air) as the terminal oxidant to afford the corresponding dihydroisoquinoline derivative in 44% yield.^[5a] This lack of precedents of catalytic protocols is striking considering that the resulting dihydroisoquinoline (DHIQ) skeleton is an interesting motif present in natural products and a versatile scaffold for alkaloid syntheses.^[9,10]

The scarcity of studies involving benzylamine derivatives in Co-catalyzed C–H functionalization^[11] may be attributed to their propensity to undergo dehydrogenation at the benzylic position under oxidative conditions, potentially leading to imine-type intermediates and/or aromatization of the final products.^[12] We speculated that the combination of Co-catalyst with oxygen as smooth oxidant could enable an efficient access to DHIQ derivatives via annulation of benzylamine derivatives with alkynes, thus expanding the synthetic utility of this reaction while moving towards sustainable development. During the preparation of this manuscript, Cui reported a Co(OAc)₂-catalyzed picolinamide-directed annulation of benzylamine derivatives with alkynes using a 50 mol% of catalyst loading and O₂ as terminal oxidant.^[13] In this report, dehydrogenation at the benzylic position occurs concomitantly to the annulation process, resulting in the formation of isoquinolines. Herein we present an operationally simple and structurally flexible procedure for the synthesis of a variety of DHIQ, including chiral, non-racemic derivatives. Important mechanistic insights including isolation and interception of some presumed Co-species involved in the catalytic cycle are also provided.

Results and Discussion

Optimization studies. The model reaction between the parent *N*-benzylpicolinamide (**1**) and 4-octyne was chosen for optimization studies (Table 1). In accordance with the above mentioned precedents,^[8,11] poor outcome obtained in the initial experiment using Co(OAc)₂ (20 mol %) in conjunction with Mn(OAc)₂ (2 equiv) as cooxidant and NaOAc (4 equiv) as a base under oxygen atmosphere, affording product **2** in 13% GC yield

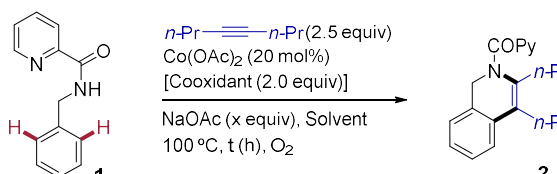
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(entry 1). Nevertheless, the reaction was very clean, with no other byproducts detected. In the absence of NaOAc the catalytic activity was virtually suppressed (5% GC yield, entry 2), suggesting that an extra-source of acetate ions is necessary for the reaction to proceed. To our satisfaction, the conversion was dramatically improved in the absence of any oxidant other than oxygen, allowing the isolation of **2** in 77% yield (entry 3). Furthermore, oxygen as terminal oxidant is crucial for this reaction, given that only traces of **2** could be detected in the absence of both Mn(OAc)₂ and oxygen (degassed solvent, entry 4). As expected, no product was detected when the reaction was performed in the absence of cobalt catalyst (entry 5). A solvent screening (entries 6-11) revealed that ethanol, 1,4-dioxane and DCE are suitable for this transformation (80-84% GC yield), while HFIP failed to provide **2** in useful conversion (16% GC yield, entry 8).

Table 1. Optimization studies in the model reaction of **1** with 4-octyne^[a]



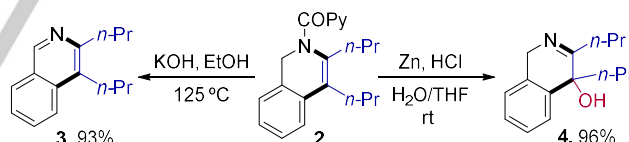
Entry	Cooxidant	NaOAc (equiv)	Solvent	Time (h)	2 (%) ^[b]
1	Mn(OAc) ₂	4.0	TFE	12	13
2	Mn(OAc) ₂	0	TFE	12	5
3	–	4.0	TFE	12	85 (77) ^[c]
4 ^[d]	–	4.0	TFE	12	<5
5 ^[e]	–	4.0	TFE	12	<5
6	–	4.0	TFE	4	85
7	–	4.0	EtOH	4	83
8	–	4.0	HFIP	4	16
9	–	4.0	DCE	4	80
10	–	4.0	1,4-Dioxane	4	84
11	–	4.0	<i>p</i> -Xyle ^[c] ne	4	4
12 ^[f]	–	1.5	EtOH	2.5	92 (85) ^[c]
13	–	1.0	EtOH	2.5	79
14	–	0.5	EtOH	2.5	22
15 ^[g]	–	1.5	EtOH	2.5	70
16 ^[h]	–	1.5	EtOH	12	80 (70) ^[c]

[a] **1** (0.15 mmol, 1.00 equiv), 4-octyne (0.37 mmol, 2.50 equiv), Co(OAc)₂ (20 mol%), cooxidant (2.00 equiv), NaOAc (x equiv), solvent (1 mL), O₂ (1 atm), 100 °C, t (h). [b] GC yields (*n*-hexadecane as internal standard).

[c] Isolated yield upon chromatographic purification. [d] Degassed solvent. [e] In the absence of Co-salt. [f] 4-Octyne (0.22 mmol, 1.50 equiv), Co(OAc)₂ (15 mol%). [g] 80 °C. [h] Scale-up to 1.5 mmol of **1**.

Using EtOH as solvent, we sought to enable lower catalyst loading and decrease the excess of both alkyne and base. After minor adjustments, it was found that product **2** can be obtained in 85% isolated yield within just 2.5 hours with 15 mol% of Co-catalyst in the presence of 1.5 equiv of alkyne and 1.5 equiv of NaOAc (entry 12), which were set up as the optimized conditions. The essential role of acetate for catalyst turnover was verified by lowering NaOAc loading to 1.0 and 0.5 equiv and observing a significant decrease in the yield of **2** (79% and 22% GC yield, entries 13 and 14, respectively). We also found a small decrease in reactivity when the reaction temperature was reduced to 80 °C (entry 15). Finally, this method allows for scale-up to 1.5 mmol with no appreciable loss of efficiency, which is important for practical convenience (entry 16).

Chemoselective deprotection and removal of the auxiliary COPy group. In accordance with our desired goal of accessing DHIQ, conditions for the efficient removal of the picolinamide auxiliary without aromatization of the heterocyclic ring were needed. Under the commonly employed basic conditions (KOH in EtOH at 125 °C), deprotection/aromatization took place efficiently to provide the isoquinoline derivative, as illustrated in the transformation of **2** into **3** (93% yield, Scheme 1). Instead, *N*-deprotection without aromatization proved to be feasible by changing to reductive acidic conditions.^[14] In the presence of Zn/AcOH, the resulting unprotected enamine undergoes a facile benzylic oxidation by atmospheric O₂ to afford the 4-hydroxy-1,4-dihydroisoquinoline **4**. This oxidation of 1,2-DHIQ derivatives had been documented in the literature.^[15]



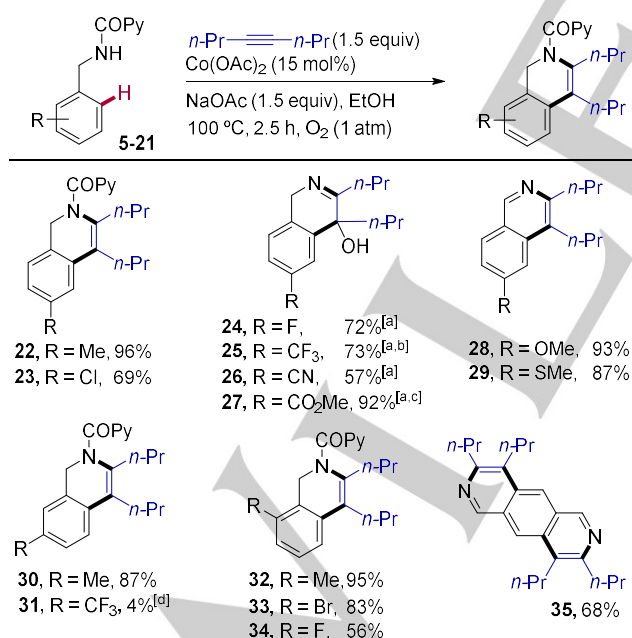
Scheme 1. *N*-Deprotection of **2**.

Evaluation of the substitution at the *N*-benzylpicolinamide substrate. Encouraged by these results, we next evaluated the scope of the C–H/N–H annulation of various benzylamine derivatives with 4-octyne (Scheme 2). A broad range of *p*-substituted derivatives underwent annulation reaction in acceptable to good yields (products **22–29**, 57–96%) with no remarkable sensitivity to the electronic characteristics of the substituent (OMe, SMe, Me, Cl, F, CF₃, CN, CO₂Me). Eventually, the crude reaction mixture can be subjected to the *N*-deprotection procedure under Zn/HCl accompanied by spontaneous oxidation by air to afford the corresponding 4-hydroxy-1,4-DHIQ derivatives in useful overall yields (products **24–27**, 57–92%). It is also worth mentioning that those substrates bearing a OMe or a SMe substituents led to the *in situ* formation of the corresponding fully aromatic isoquinoline derivatives in the

Co-catalyzed annulation step (**28** and **29**, respectively). The reason behind this different behavior is not clear at the present time.

In contrast, the electronic effects of the *meta*-substituents appear to have more influence over the reactivity than do the substituents at *para*-position. For example, whereas a *meta*-Me benzylamine derivative provides the corresponding DHIQ product **30** in high yield (87%), the presence of a strong electron-withdrawing CF₃ substituent at *meta*-position decreased the yield significantly (**31**, 4% GC yield). The functionalization took place at the more sterically accessible *ortho*-C–H bond of the *meta*-substituted benzylamine, the DHIQ being obtained as a single regioisomer (see SI for structure determination). In contrast to many reported methods in which an *ortho*-substituent retards or shuts down the reaction completely, this transformation showed no appreciable sensitivity to steric hindrance in the aryl *ortho*-position (**32–34**, 56–95%). Slightly reduced reactivity was observed in the case of an electron withdrawing *ortho*-F substituent, yet the corresponding DHIQ **34** was obtained in a synthetically useful 56% yield.

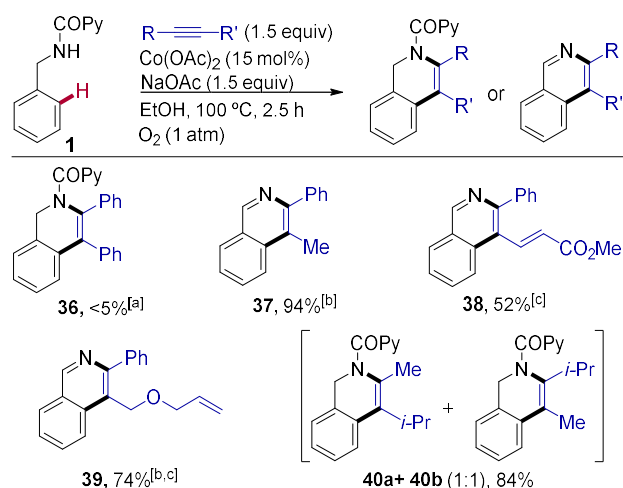
Overall, it is important to stress the considerable chemoselectivity offered by this catalyst system, tolerating substrates bearing a range of useful functionalities, including halides (F, Cl and Br) and the potentially coordinating SMe and CN moieties. Even a twofold C–H functionalization/alkyne annulation was feasible in the case of using a 1,4-phenylenedimethanamine derivative, resulting in the direct construction of a polyheteroaromatic pyrido[3,4-*g*]isoquinoline skeleton (**35**, 68%) under the reaction conditions.



Scheme 2. Evaluation of the substitution at the *N*-benzylpicolinamide substrate. [a] Overall yield for the annulation / *N*-deprotection steps. [b] $\text{Co}(\text{OAc})_2$ (20 mol%), 12 h. [c] 1,4-dioxane as solvent and heating at 110 °C for 12 h. [d] Detected by GC.

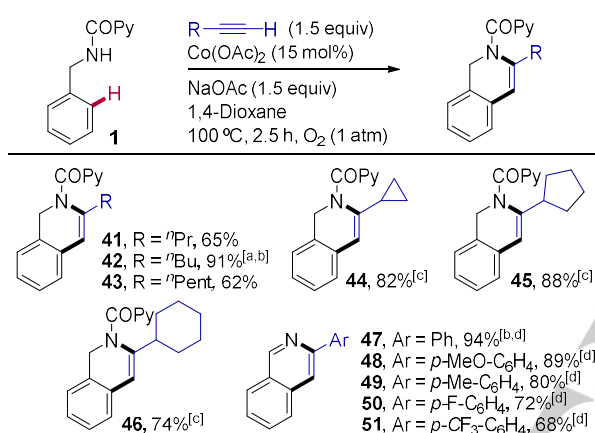
Co-catalyzed C–H alkenylation/annulation of benzylamine **1 with internal alkynes.** To study the alkyne substrate scope, several types of internal alkynes were surveyed in the reaction with *N*-benzylpicolinamide **1** (Scheme 3). Unfortunately, a diaryl-substituted alkyne such as diphenylacetylene was found to be unsuitable for this set of conditions (**36**, <5% GC yield). Interestingly, this reactivity was opposite to that observed in our previously reported Rh-catalyzed C–H functionalization of picolinamides with alkynes, in which diarylacetylenes displayed excellent reactivity whereas dialkyl-alkynes resulted in a total lack of reactivity.^[16] This, along with the different reaction outcome observed, highlights the complementarity between Rh-catalysis and Co-catalysis.

Unsymmetrical internal alkynes represents a greater challenge due to their inherent difficulty to achieve useful regiocontrol in the 1,2-migratory insertion step. We were pleased to find that the reaction with conjugated 1-aryl-1-alkynes such as 1-phenyl-1-propyne occurred smoothly to afford the corresponding isoquinoline **37** as a single regioisomer, in which the aryl substituent is regioselectively placed proximal to the nitrogen atom (Scheme 3, 94% yield). Other conjugated alkynes with electronically dissimilar acetylenic substituents did also participate in the coupling reaction maintaining the level and sense of regioselectivity, to provide the corresponding isoquinoline derivatives (products **38** and **39**, 52% and 74%, respectively). In these cases, the intermediate DHIQ product could not be isolated, which seems to indicate that the use of conjugated alkynes as the coupling partner favors the aromatization/*N*-deprotection of the heterocyclic ring leading to the isoquinoline product rather than the DHIQ. Accordingly, a mixture of DHIQ regioisomers was observed with a sterically biased internal dialkyl-alkynes such as isopropyl methyl acetylene, albeit with virtually no regiocontrol (**40a+40b**, 84%). This result suggests that the regioselectivity of insertion appears to be dictated mainly by electronic factors rather than steric factors.



Scheme 3. Co-catalyzed C–H alkenylation/annulation of benzylamine **1** with internal alkynes. [a] Determined by GC. [b] Regiochemistry determined by NOESY experiments. [c] Using 1,4-dioxane as solvent.

Co-catalyzed C–H annulation with terminal alkynes. A limitation frequently encountered in rhodium(III)- and ruthenium(II)-catalyzed oxidative synthesis of nitrogen-containing heterocycles is the inability to incorporate terminal alkynes due to the problematic alkyne dimerization.^[17] It is, therefore, noteworthy that a variety of terminal alkynes with both alkyl and aryl substitution reacted smoothly under these Co-catalyzed conditions, affording in good yields as single regioisomers the corresponding 1,2-DHIQ in the case of alkyl-alkynes (Scheme 4, **41–46**, 62–91%) or the corresponding isoquinolines in the case of aryl-alkynes (**47–51**, 68–94%). In all cases studied the alkyl or aryl acetylenic substituent ends up distal to the nitrogen atom (at C4) in the DHIQ skeleton. Conjugated aryl-alkynes worked effectively in the absence of NaOAc as additive.

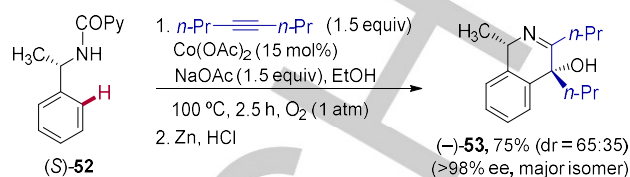


Scheme 4. Co-catalyzed C–H annulation with terminal alkynes. [a] $Co(OAc)_2$ (10 mol%), NaOAc (40 mol%). [b] Regiochemistry determined by NOESY experiments. [c] 20 mol% NaOAc. [d] In absence of NaOAc.

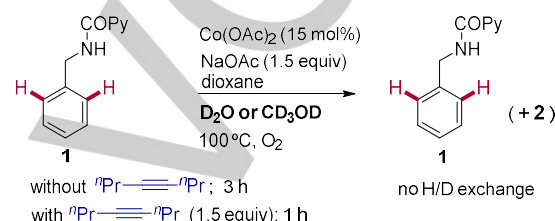
Tolerance towards substitution at the benzylic position and preservation of stereochemical integrity. To test whether this annulation protocol would be sensitive to substitution at the benzylic position and whether the stereochemical integrity of a stereogenic center at such position would be preserved, the enantiopure (S)- α -methylbenzylamine derivative (**S**)-**52** was subjected to the standard conditions and subsequent *N*-deprotection with Zn/HCl (Scheme 5). Pleasingly, the resulting 4-hydroxy-1,4-DHIQ (–)-**53** was obtained in good yield (75%) and no appreciable loss of enantiopurity (>98% ee, major diastereoisomer), yet with moderate diastereoselectivity ($dr = 65:35$). The stereochemical assignment of **53** was tentatively established by NOESY experiments (see SI for details).

Mechanistic insights. Deuterium labelling studies. We next performed a series of experiments to gain some insights into the mechanism (Scheme 6). First, reactions with isotopically labeled co-solvents (D_2O or CD_3OD) in both the presence and absence of the alkyne coupling partner, showed no deuterium incorporation at either the recovered unreacted starting material or at the DHIQ product **2**. This lack of H/D scrambling suggests

that the reaction may proceed through an irreversible cyclometalation pathway.^[18]



Scheme 5. Tolerance towards substitution at the benzylic position and preservation of stereochemical integrity.



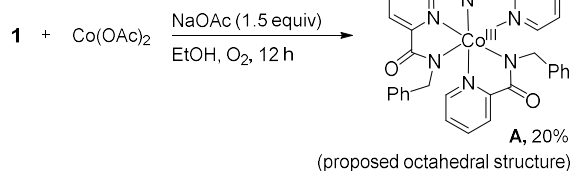
Scheme 6. D-Labeling experiments.

Kinetic studies. Next, we focused on the reaction rate dependences on the catalyst and the reagents concentrations in the model coupling between **1** and 4-octyne under optimized conditions (see SI for details).^[19] The reaction exhibited a first order kinetic dependence with respect to cobalt concentration, suggesting a mononuclear species as active catalyst. Reaction rate *versus* time curve revealed a significant induction period of 25 min.^[5a] Nonetheless, during the portion of the reaction that exhibits steady state behavior, the rate of the annulation was found to be zeroth-order with respect to the alkyne, suggesting that the alkyne is not involved in the rate-determining step. The reaction showed a partial negative order in the benzylamine derivative concentration, which can be plausibly ascribed to off-cycle nonproductive binding interactions between this species and the catalyst prior to the C–H cleavage, thereby decreasing the effective concentration of catalyst. A similar behavior of the negative-order rate dependence on substrate has also been observed in recent related literature on Co-catalysis.^[20]

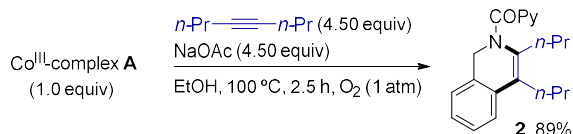
Isolation of a Co-complex and study of its competency. To gain insight about possible intermediates during the reaction course, we explored the reaction of equimolar amounts of **1** and $Co(OAc)_2$ in the presence of NaOAc (1.5 equiv) in EtOH under O_2 atmosphere at 100 °C for 12 hours (Scheme 7a). In this reaction we could isolate the air-stable Co^{III} -complex **A** (20%), which was characterized through ESI-HRMS and NMR analysis upon chromatographic purification (see SI). Unfortunately, no suitable crystals for X-ray diffraction analysis could be obtained for this complex. In Co^{III} -complex **A**, three units of **1** are coordinated to the metal center as monoanionic bidentate *N,N*-donor ligands. It may be noted that cobalt undergoes a one-electron oxidation ($Co^{II} \rightarrow Co^{III}$) during the complex formation in which oxygen appears to have served as the oxidant.^[21]

Interestingly, Co-species **A** smoothly reacted with 4-octyne to afford the DHIQ derivative **2** as the only product in good yield (89%, Scheme 7b). Furthermore, complex **A** was found to be catalytically competent in the reaction of **1** with 4-octyne, providing **2** in good yield (Scheme 7c), suggesting that this complex could be an active catalyst precursor for this reaction.

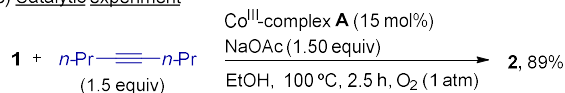
a) Isolation of Co-complex **A**



b) Stoichiometric experiment



c) Catalytic experiment



ESI-HRMS experiment. ESI-HRMS experiment shed some more light on the nature of the presumed Co-complexes that were formed in the reaction of **1** with 4-octyne under the optimized catalytic conditions. The mass spectrum of the crude reaction mixture upon 45 min (Figure 1) was quite clean, with a dominant molecular ion peak of DHIQ **2** ($m/z=343.1778$). Interestingly, four peaks could be assigned to Co-complexes. The peak at $m/z=693.1991$ corresponds to Co^{III}-complex **A** previously isolated (calculated value: $m/z=693.2019$). The peak at $m/z=775.1922$ was assigned to Co^{III}-complex **B** (theoretical value: $m/z=775.2050$, M+Na⁺), which keeps the three units of picolinamide ligand in the coordination sphere of Co, but one of which is now coordinated as a monodentate neutral ligand (rather than in a bidentate monoanionic fashion), with an acetate occupying the vacant site. The peak at $m/z=563.1093$ was assigned to Co^{III}-complex **C** (theoretical value: $m/z=563.1099$, M+Na⁺), holding two units of **1** as ligands and an acetate bonded to the metal (the latter likely in a bidentate fashion). Presumably, complex **C** results from complex **A** through ligand displacement via complex **B**. Interestingly, a minor peak **D** at $m/z=481.0991$ was also observed, whose mass would correspond to the five membered cobaltacycle presumably formed from **C** upon *ortho*-C–H functionalization (Co^{III}-complex **D**, consistent with the theoretical value $m/z=481.1069$).^[22a]

Scheme 7. Isolation of a preformed Co-complex and study of its competency.

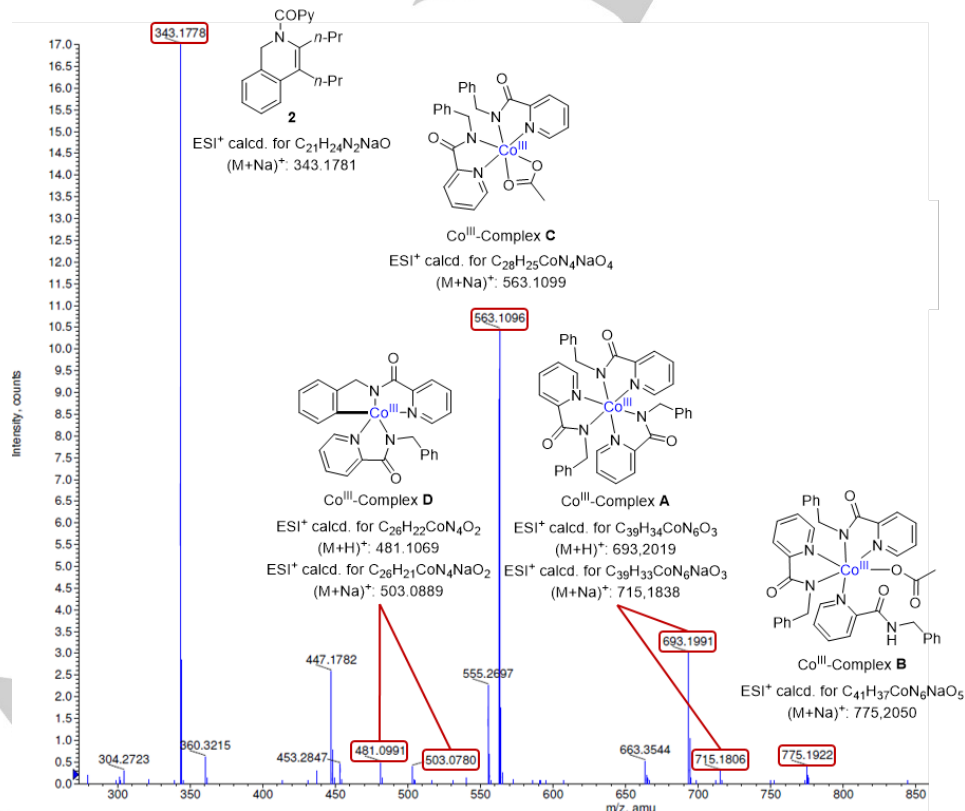
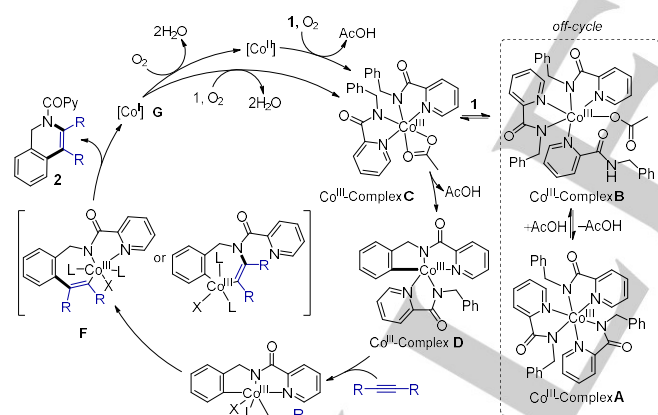


Figure 1. Key area of the ESI-HRMS spectrum of the crude reaction mixture between **1** and 4-octyne after 45 min.

Plausible mechanistic hypothesis. Taking together all these experimental observations and current literature,^[7,22] a plausible simplified mechanism is depicted in Scheme 8. Initial coordination of **1** to Co(OAc)₂ species with concomitant oxidation of cobalt(II) by oxygen (dissolved in solution)²¹ would generate the presumed active Co^{III} species **C**, in equilibrium with Co^{III} complex **A** via complex **B**. In fact, complex **A** may function as a reversible off-cycle reservoir that could explain the partial negative order for the substrate **1** previously observed in kinetic studies. Acetate-assisted *ortho*-C–H bond functionalization would lead to the coordinatively unsaturated 16-electron Co^{III} complex **D**. Alkynyl coordination (**E**) and subsequent 1,2-migratory insertion of the cobalt-carbon bond across the alkyne would result in the formation of the seven-membered alkenyl-cobalt intermediate **F**. Subsequent reductive elimination step releases the 1,2-DHIQ product while the concomitantly formed Co^I species is reoxidized by O₂ to regenerate the Co^{II} and/or Co^{III} species, thus closing the catalytic cycle. The relative ease of forming the off-cycle tris-picolinamide chelate Co^{III} complexes of type **A**, which should be less favorable in the case of using the more-hindered 8-quinolinamide substrates, could explain the higher reactivity of the latter substrates over picolinamide derivatives^[8] and the use of high catalyst loadings^[8,13] described in previous reports. Interestingly, the excess of acetate ions seems to counteract the formation of tris-picolinamide chelate Co^{III} complexes of type **A** by promoting ligand displacement to form complexes of type **C**.



Scheme 8. Proposed catalytic cycle.

Conclusions

In conclusion, we have developed a sustainable and operationally simple Co-catalyzed C–H alkenylation/annulation of benzylamine derivatives with both terminal and internal alkynes that enables the access DHIQ structures. This method relies on simple Co(OAc)₂ as precatalyst and O₂ as the sole terminal oxidant and features high selectivity and broad functional group tolerance. The reaction is tolerant of substitution at the benzylic position, with no appreciable loss of

enantiomeric purity when starting from chiral non-racemic substrates, thereby allowing the preparation of chiral, non-racemic DHIQ derivatives. Mechanistic studies including kinetic analysis, labelling studies, Co-complex isolation and HRMS-interception provided valuable insights about the reaction course and the structure of some presumed Co-species involved in the catalytic cycle.

Experimental Section

Representative procedure for Co-catalyzed C–H alkenylation-annulation:

The conversion of *N*-benzylpicolinamide (1**) into [(3,4-dipropylisoquinolin-2(1*H*)-yl)(pyridin-2-yl)methanone] (**2**):** An oven-dried, nitrogen-flushed 10 mL vessel was charged with *N*-benzylpicolinamide (**1**) (31.8 mg, 0.15 mmol, 1.00 equiv), cobalt(II) acetate (3.98 mg, 0.023 mmol, 0.15 equiv) and sodium acetate (18.5 mg, 0.23 mmol, 1.50 equiv). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with oxygen. Under the atmosphere of oxygen, ethanol (1.00 mL) and 4-octyne (33.0 μ L, 0.23 mmol, 1.50 equiv) were added *via* syringe. The resulting mixture was then stirred at 100 °C for 2.5 h before it was quenched with a saturated solution of potassium tartrate (5.00 mL) and extracted with EtOAc (2 x 5.00 mL). The organic layer was washed with brine (5.00 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (CH₂Cl₂-Et₂O 20:1) to afford **2** as a colorless oil (42.7 mg; 89%; see the Supporting Information for spectroscopic data).

Representative procedure for the deprotection of the picolinamide group with KOH:

The conversion of [(3,4-dipropylisoquinolin-2(1*H*)-yl)(pyridin-2-yl)methanone] (2**) into 3,4-dipropylisoquinoline (**3**):** An oven-dried, nitrogen-flushed 20 mL vessel was charged with **2** (48.0 mg, 0.15 mmol, 1.00 equiv) and KOH (504 mg, 9.00 mmol, 60.0 equiv). The reaction vessel was sealed with a Teflon lined cap, and ethanol (3.00 mL) was added *via* syringe. The resulting mixture was stirred at 125 °C for 24 h before it was cooled down to room temperature, diluted with ethyl acetate and washed with water. The organic phase was separated, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane-EtOAc-CH₂Cl₂ 5:1:1), to give **3** as a yellow oil (29.7 mg; 93%; see the Supporting Information for spectroscopical data).

Representative procedure for the deprotection of the picolinamide group with Zn/HCl:

The conversion of [(3,4-dipropylisoquinolin-2(1*H*)-yl)(pyridin-2-yl)methanone] (2**) into 3,4-dipropyl-1,4-dihydroisoquinolin-4-ol (**4**):** To a suspension of **2** (48.0 mg, 0.12 mmol, 1.00 equiv) in a mixture of H₂O (3 mL) and THF (1 mL) was added 12 M HCl (0.30 mL, 30.0 equiv) and the mixture was stirred for 5 minutes at room temperature. Zinc dust (118 mg, 1.80 mmol, 15.0 equiv) was then added in three portions and the mixture was stirred at room temperature until consumption of **2**. Then, the reaction was mixed with ca. 200 mg of sand and filtered through a celite plug. The filtrate was transferred to a separatory funnel with 2M NaOH (2 x 20 mL) and extracted twice with dichloromethane (2 x 20 mL). The combined organic phase was dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane-EtOAc-CH₂Cl₂ 5:1:1), to give **4** as a white oil (31.1 mg; 96%; see the Supporting Information for spectroscopical data).

Acknowledgements

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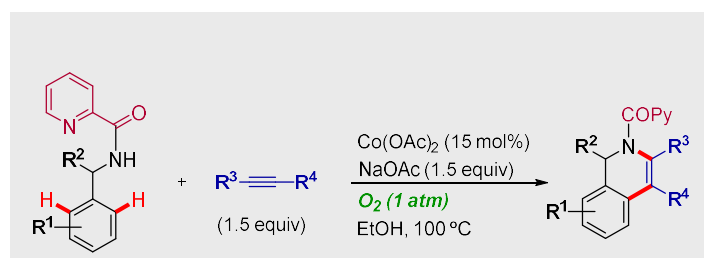
Keywords: cobalt • alkenylation/annulation • alkyne • picolinamide • dihydroisoquinoline

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FULL PAPER



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**Cobalt-Catalyzed *ortho*-C–H
Functionalization/Alkyne Annulation
of Benzylamine Derivatives: Access
to Dihydroisoquinolines**

Molecular O_2 as the sole oxidant and simple $Co(OAc)_2$ as precatalyst are key features of a practical procedure for the C–H alkenylation/annulation of benzylamine derivatives with both internal and terminal alkynes, thereby enabling the access to dihydroisoquinolines, including chiral, non racemic derivatives. Valuable insights about the reaction course and presumed Co-species involved in the catalytic cycle are provided.