Cobalt-Catalyzed bis-Borylation of Quinolines: The Importance of the Cobalt Triplet State

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RESEARCH ARTICLE

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Dedicated to Dr. Corinne Aubert for her outstanding contribution to cobalt chemistry on the occasion of her retirement.

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Abstract: We report herein a mild stereo- and regioselective dearomatization of quinolines using the simple low valent $HCo(N_2)(PPh_3)_3$ complex that exhibits labile ligands. Conditions to form selectively, at room temperature, high-valued 1,4-bis-borylated tetrahydroquinolines from simple starting heteroaromatic compounds have been developed. The efficient and selective functionalization of a large scope of quinolines bearing various electron-donating or electron-withdrawing substituents is presented, as well as the post-modification of the resulting C–B bond. NMR and labelling studies are consistent with a cascade mechanism pathway, starting from an *in situ* generated paramagnetic bis-quinoline cobalt(I) hydride complex. A first quinoline dearomatization followed by a cobalt(I)-catalyzed Markovnikov hydroboration of the remaining double bond allows the introduction of the boronic ester group only at C4 position. DFT calculations particularly highlight the importance of the cobalt triplet state throughout the reaction pathway, and bring some rationalization for the observed C4 selective borylation.

Introduction

The tetrahydroquinolines (THQs) structural units are found in numerous natural products that exhibit a variety of biological activities.[1] Among them the 4-substituted tetrahydroquinolines have recently attracted attention with, for instance, the natural 4-phenyl-3,4-dihydroquinolone (aflaquinolone derivatives)[2] but also some anti-HIV,[3] antifungal,[4] antiparasitic[5] and anticancer[6] molecules (**Figure 1**). If several synthetic strategies such as the Povarov cyclization,[1,7] C−H functionalization,[8] or Michael addition[9] have been developed with success, the selective dearomatization of quinoline towards tetrahydroquinoline appears the most direct one. This field has attracted a great deal of interest these past few years and while selective methodologies based on hydrosilanes and hydroboranes as mild reducing agents are now well developed,[10] the use of earth-abundant metals such as cobalt is still limited. The same year, Geetharani[11] and our group[12] reported respectively the 1,2-hydroboration and 1,2-hydrosilylation of *N*-heteroarenes (see **Scheme 1a**).[13]

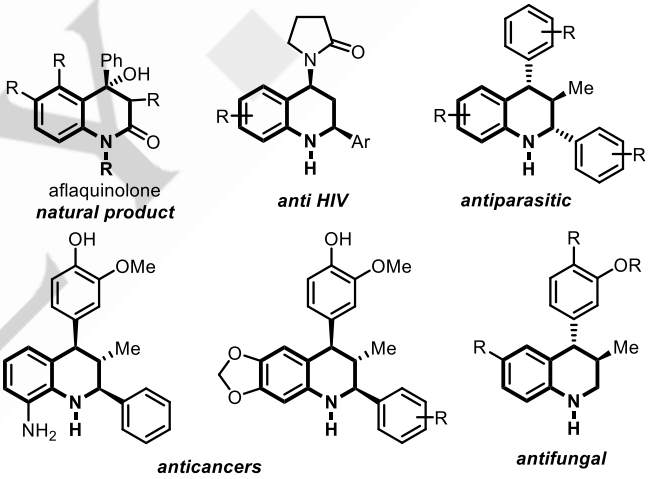
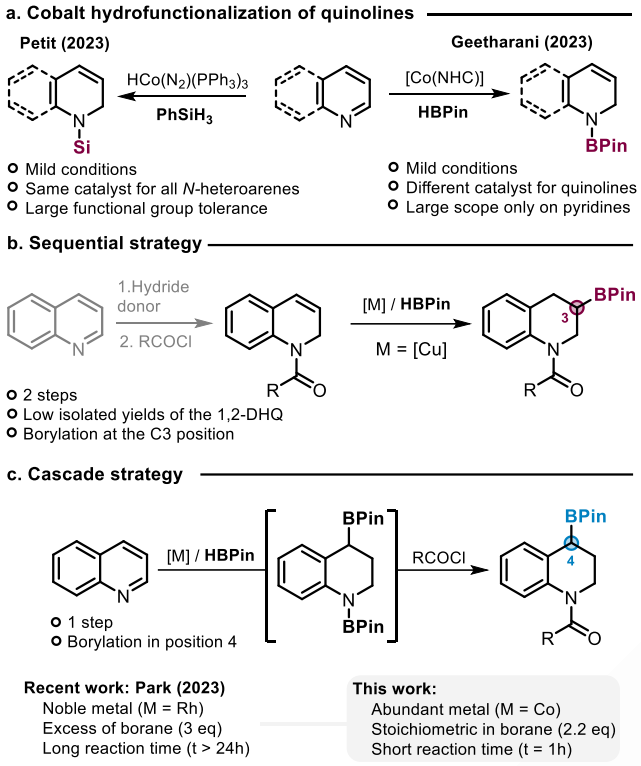


Figure 1. Representative activity of 4-substituted tetrahydroquinolines

On the other hand, despite huge progress, the site-selective introduction of substituents onto quinoline rings to synthesize substituted THQs remains a difficult task that has been barely addressed yet.[14] The sequential strategy reported by Ito[15a,b] and later by Hou and Zhang[15c] for the hydroboration of the 1,2-dihydroquinoline (1,2-DHQ) led to the borylation at the C3 position (see **Scheme 1b**). It is noteworthy that this two-steps synthesis requires the isolation and protection of the sensitive 1,2-DHQ intermediate which is generally achieved in low yields.[15] Following our study on the selective hydrosilylation of *N*-heteroarenes using the very simple well-defined $HCo(N_2)(PPh_3)_3$ **Co-1**,[12] we envisioned replacing the silane partner by a borane to selectively reach the *N*-borylated 1,2-DHQ. Given that Chirik described in 2015 the selective Markovnikov hydroboration of indenes and styrenes using the same complex **Co-1**,[16] we wondered whether it would be able to promote the challenging one-pot cascade: dearomatization of quinoline /

regioselective hydroboration of the remaining double bond[16a] (see **Scheme 1c**).



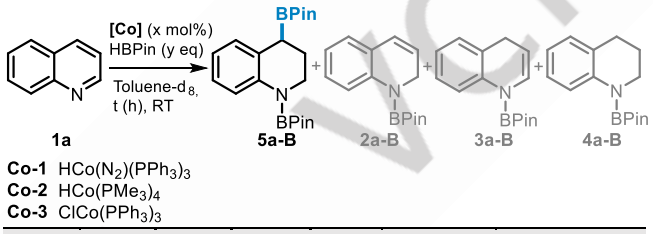
Scheme 1. Hydroelementation of quinolines with cobalt catalysts and synthesis of borylated tetrahydroquinolines

During our investigation Park reported an elegant work based on a similar strategy using a rhodium catalyst with an excess of pinacolborane.[17] Herein we describe a sustainable cascade consisting of a bis-borylation of quinolines using the simple well-defined low valent cobalt complex **Co-1** at low temperature in a short reaction time with no excess of pinacol borane.

Results and Discussion

In line with our work on low-valent cobalt catalysis[18] and more specifically on quinoline hydrosilylation,[12] we first investigated the selective 1,2-borylation of quinoline using 1 equivalent of pinacol borane in presence of 2 mol% of **Co-1** (Entry 1, **Table 1**). We observed by NMR monitoring a mixture of the known borylated 1,2-DHQ **2a-B**, 1,4-DHQ **3a-B** and THQ **4a-B** as well as a new bis-borylated compound **5a-B**. Increasing the amount of HBpin to 2 equivalents led to a full conversion of the starting quinoline in only 1 hour at room temperature with 40% yield for the product of interest **5a-B** (entry 2). Further increase to 3 and 5 equivalents had only a slight effect since 44% and 45% of **5a-B** were obtained respectively (entries 3 and 4). In addition, no better yield could be reached by doubling the reaction time (entry 5). We then studied the catalyst loading by increasing it from 2 mol% to 4 mol% which had a considerable effect since the 4-borylated tetrahydroquinoline **5a-B** was obtained as the major product of the reaction with an NMR yield of 67% (entry 6). Knowing that the amount of HBPin had no significant effect, we decreased it to 2.2 equivalents and we were delighted to see that similar NMR yield of **5a-B** was obtained with the total disappearance of the 1,2-DHQ **2a-B** (entry 7). Finally, increasing the catalyst loading to 6 mol% gave full conversion of the starting quinoline with a ratio of 78% of **5a-B** and 18% of **3a-B** (entry 8). It is worth mentioning that using the related cobalt complex $HCo(PMe_3)_4$ **Co-2** at 110°C gave full conversion but this time with the selective formation of **2a-B**, even by using 3 equivalents of HBpin (entry 9). Finally, $ClCo(PPh_3)_3$ **Co-3** at 25°C gave 37% of **2a-B** after 1h and a mixture of products with 8% of **5a-B** when the reaction was pursued for 72h (entry 10).

Table 1. Optimization of the reaction conditions[a]

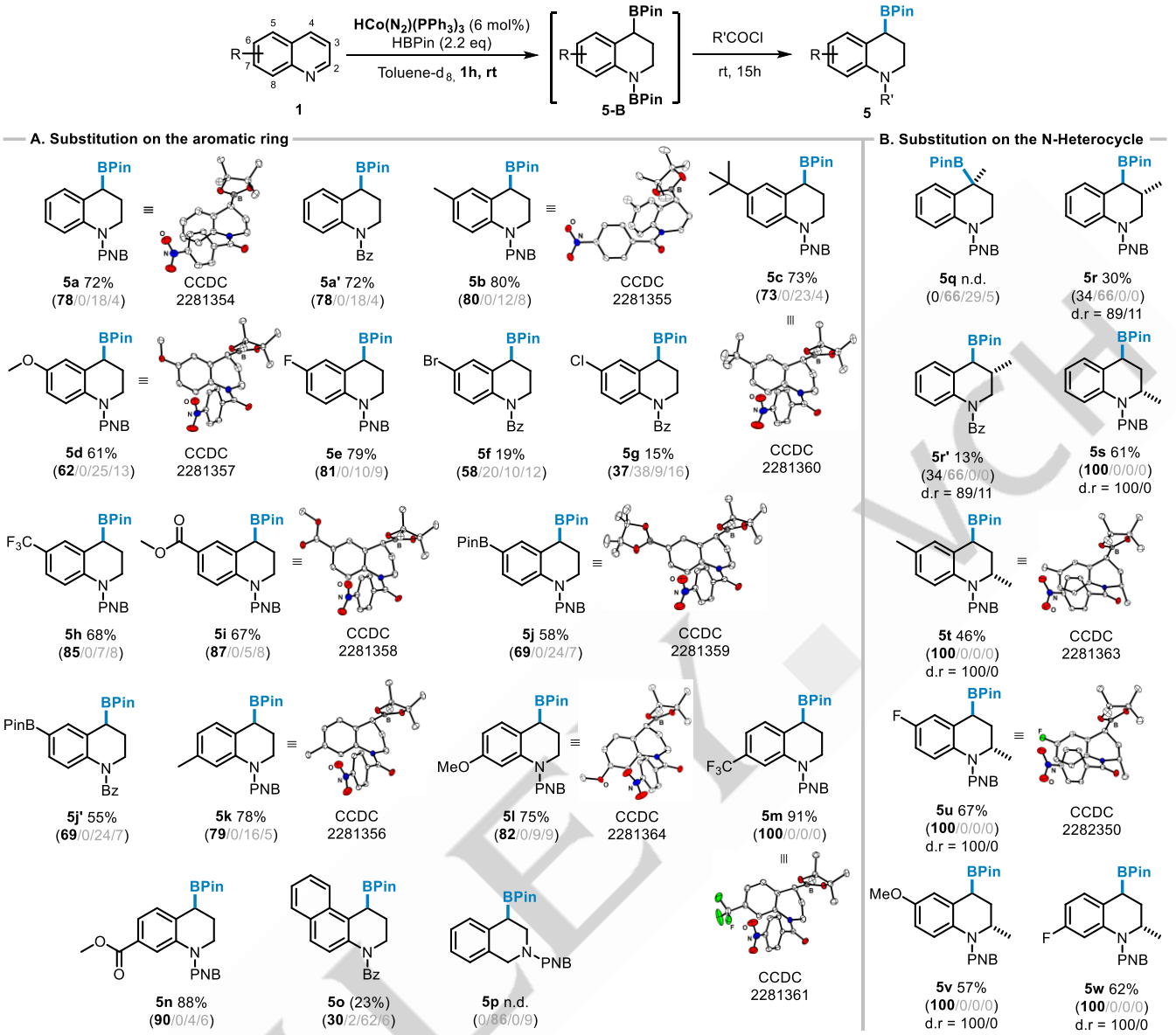


Co-1 $HCo(N_2)(PPh_3)_3$
Co-2 $HCo(PMe_3)_4$
Co-3 $ClCo(PPh_3)_3$

Entry	y (eq)	[Co]	x (mol%)	Time	Conv.[b]	Ratio (**5a**/2a/3a/4a)-**B**[b]
1	1	**Co-1**	2	1	72%	**15**/16/36/5
2	2	**Co-1**	2	1	100%	**40**/45/8/7
3	3	**Co-1**	2	1	100%	**44**/43/5/8
4	5	**Co-1**	2	1	100%	**45**/44/5/6
5	5	**Co-1**	2	2	100%	**42**/39/14/5
6	5	**Co-1**	4	1	100%	**67**/17/7/9
7	2.2	**Co-1**	4	1	100%	**63**/0/32/5
8	2.2	**Co-1**	6	1	100%	**78**/0/18/4
9[c]	3	**Co-2**	1	1	100%	**0**/100/0/0
10	5	**Co-3**	2	1 (72)	37% (100%)	**0**/37/0/0 (**8**/52/11/29)

[a] Reactions were performed on a 0.5 mmol scale. [b] Conversions and Ratios were determined by ^{1}H spectroscopic analysis of the crude reaction mixtures with 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction performed at 110 °C.

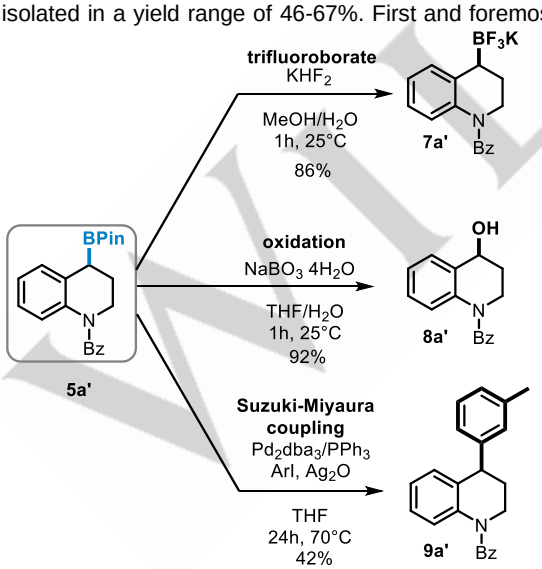
Although the bis-borylated intermediate **5a-B** could be characterized *in situ* by ^{1}H NMR spectroscopy analysis using a J. Young NMR tube, it was too moisture and air sensitive to be isolated as such. Therefore, the use of 1.2 equivalents of *p*-nitrobenzoyl chloride (PNB-Cl) or benzoylchloride (Bz-Cl) allowed us to easily purify by silica gel chromatography the desired products **5a** or **5a'** that were isolated with an overall yield of 72% over the two steps (**Scheme 2**). At this stage, we also managed to obtain some crystals of **5a** that were suitable for X-Ray diffraction analysis. We were thus able to confirm the regioselectivity of the hydroboration with the presence of the boron atom at the C4 position. With these standard conditions in hands (Entry 8, **Table 1**) and an efficient protecting method to isolate the 4-borylated tetrahydroquinoline **5a**, we then investigated the scope of substrates (**Scheme 2**).



Scheme 2. Scope of the quinolines. A. Variation of the substituents on the benzenic ring. B. Variation of the substituents on the heterocycle. Conversions (100%) and ratios of (**5/2/3/4**)-**B** measured by ^{1}H NMR spectroscopy analysis on the signal of the protons in the C2 position. For **5s**, **5t** and **5v** conversions are respectively 79, 51 and 48%. n.d.: non detected. For crystal structures thermal displacement ellipsoids are shown at 30% probability and all hydrogens atom have been omitted for clarity.

Every bis-borylated intermediates **5-B** as well as the ratio of the different products (in grey in **Scheme 2**) were characterized *in situ* by ^{1}H NMR spectroscopy analysis at the end of the reaction before protection, by collecting an aliquot and dissolving it in Toluene-d_8 (**See SI**). We first studied the influence of the substitution on the phenyl part of the quinoline. Substitutions at C6 were well tolerated and quinolines bearing an alkyl substituent such as a methyl or the more hindered *tert*-butyl were fully converted. Borylated tetrahydroquinolines **5b** and **5c** were isolated in 80% and 73% yields respectively. The electron-donating methoxy group at C6 only slightly decreased the yield to 61% for **5d**. If the 6-fluoroquinoline **1e** led to the borylated tetrahydroquinoline **5e** in a good isolated yield of 79%, its chlorinated and brominated analogues gave rise to oxidative addition into to C–X bond leading to poorer yields of 19% and 15% of **5f** and **5g** respectively which is consistent with the results obtained using $ClCo(PPh_3)_3$ **Co-3** (Entry 10, **Table 1**). Indeed, the same $XCo(PPh_3)_3$ catalysts might be formed after oxidative addition/reductive elimination. Electron-withdrawing groups were also well tolerated at C6. The trifluoromethyl and methylcarboxylate ones drove to the desired products **5h** and **5i** with an isolated yield of 68% and 67% respectively. The 6-pinacolboranequinoline **1j** could also be efficiently dearomatized and protected either with *p*-nitrobenzoyl chloride in a 58% global yield or benzoyl chloride with a yield of 55%. Substitutions at C7 were then investigated and the 7-methylquinoline **1k** led to the borylated tetrahydroquinoline **5k** in a good yield of 78%. Both electron-donating and withdrawing groups were well tolerated: the desired product **5l**, substituted by a methoxy group, was obtained in a 75% yield; compound **5m**, substituted by a trifluoromethyl group, was isolated with an excellent yield of 91%. In this case, we were delighted to observe a total selectivity toward the bis-borylated tetrahydroquinoline, as no side products were formed. The methylcarboxylate analogue

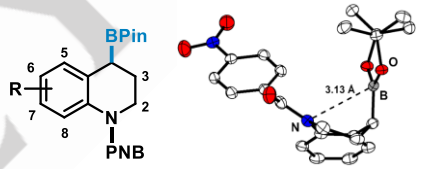
1n was efficiently transformed into **5n** with a very good overall yield of 88%. The polycyclic quinoline **1o** was fully converted, however, the major product was the 1,4-dihydroquinoline. Only 30% of the bis-borylated tetrahydroquinoline **5o-B** was observed and **5o** was isolated in 23% yield. Regarding to the isoquinoline, no bis-borylated compound **5p** was observed and the 1,2-DHQ **6p** was the major product obtained. The next step was to investigate the substitutions on the *N*-heterocyclic part, which is more challenging as it can impact either the first quinoline dearomatization step, or the subsequent hydroboration of the formed double bond. We thus evaluated the substitution in all positions from C4 to C2 (**Scheme 2B**). As expected, the borylated product **5q** substituted by a methyl group at C4 was not observed. More surprisingly, the reverse hydroboration at C3 was not observed either, only the 1,2-DHQ **2q-B** and 1,4 DHQ **3q-B** were obtained, attesting to the high regioselectivity of the second hydroboration. The substitution with a methyl group at C3 led to modest isolated yields of 30% and 13% for the 4-borylated tetrahydroquinoline (PNB or Bz) **5r** and **5r'**, showing that the second hydroboration is highly sensitive to the steric hindrance. However, this substitution at C3 prevents the isomerization from the 1,2- into the 1,4-DHQ as the 1,2-DHQ is the only side-product observed in 66% NMR yield. It is important to mention that for **5r** and **5r**' good diastereoselectivities were obtained with a ratio of 89/11 in favour of the *trans* isomers. Finally, the 2-methylquinolines, also called quinaldines, work very smoothly in our conditions at room temperature, whereas using Park's rhodium complex required an increase of the temperature.[17] This result proves that the first hydroboration is not sensitive to the steric hindrance, contrary to our previously published hydrosilylation.[12] Thus, quinaldines **1s**, **1t**, **1u**, **1v**, **1w** were selectively converted into the desired products without formation of side-products and borylated tetrahydroquinolines **5s**-**5w** were isolated in a yield range of 46-67%. First and foremost, only the



Scheme 3. Post-functionalization of **5a'**

trans-diastereoisomer was obtained, which was further confirmed by 2D NMR analysis together with the obtention of X-ray structures for **5t** and **5u**. The post-functionalization of the 4-borylated tetrahydroquinoline **5a'** was then investigated (**Scheme 3).** It was first efficiently transformed into the corresponding trifluoroborate **7a'** using KHF_2 in $MeOH/H_2O$.[20] The boronic ester could also be oxidized into the corresponding alcohol, leading to hydroxy-tetrahydroquinoline **8a'**.[21] Challenging functionalizations such as coupling reactions were then explored. The Suzuki-Miyaura cross-coupling was effective on this substrate with 3-iodotoluene as the partner, using $Pd_2(dba)_3$ as the catalyst and PPh_3 as the ligand in presence of Ag_2O as the base.[22] The resulting product **9a'** was isolated with a non-optimized yield of 42%. During this study we obtained several crystals from the different final products **5a**, **5b**, **5c**, **5d**, **5i**, **5j**, **5k**, **5l**, **5m, 5t, 5u** and **7a'** that were suitable for X-Ray diffraction analysis,[19] confirming the presence of the boron atom at C4. Surprisingly, in all the structures, the heterocyclic ring preferentially adopts a boat-like conformation with the nitrogen atom pointing towards the large boronic acid pinacol ester moiety, which is placed in axial position (**Figure 2a**). A favorable interaction may be involved to explain this unexpected geometry, characterized by a relatively short N–B distance of around 3.1Å. Interestingly, for compound **7a'** with a trifluoroborate group instead of the BPin and a benzoyl as the protecting group, this interaction no longer exists and the heterocycle adopts a more favored half-chair conformation, placing the substituted nitrogen group away from the boron atom (**Figure 2b**).

a. Crystal structure and N-B bond distances of 5:



R	Distance N···B (Å)	R	Distance N···B (Å)
H	**3.131**(3)	7-Me	**3.108**(2)
6-Me	**3.245**(5)	7-OMe	**3.104**(3)
6-OMe	**3.083**(2)	7-CF_3	**3.092**(2)
6-CO_2Me	**3.127**(3)	2-Me, 6-Me	**3.148**(2)
6-BPin	**3.086**(4)	2-Me, 6-F	**3.181**(2)
6-^{t}Bu	**3.100**(4)		

b. Crystal structure of 7a':

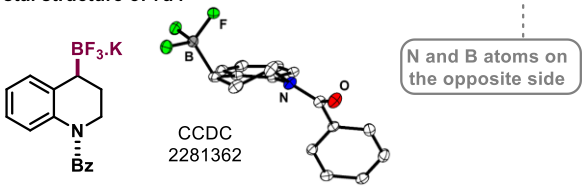


Figure 2. Crystal structures of **5a** and **7a'** and N-B bond distances for all compounds **5**. Thermal displacement ellipsoids are shown at 30% probability. Hydrogen and potassium atoms were omitted for clarity

Mechanistic investigation. We then focused our attention to the reaction mechanism. Our hypothesis was that the

reaction proceeds *via* a two-steps process where the first one would be the dearomatization of the quinoline moiety to give the *N*-borylated 1,2-dihydroquinoline **2-B**. The second step would then be the Markovnikov-hydroboration of the resulting double bond. To confirm this hypothesis, we first checked if the initial elementary step was similar to the one involved in the hydrosilylation of quinolines[12,18h] namely an oxidative addition in the hydride donor. An experiment between **Co-1** and 10 equivalents of pinacolborane HBPin in a J.Young NMR tube was conducted and analysed by ^{1}H and ^{31}P NMR spectroscopy: only a loss of triphenylphosphine was observed[23] with no evidence of oxidative addition as previously underlined by Chirik.[16b] On the contrary, when mixing **Co-1** with an excess of quinoline **1a**, the rapid disappearance of the hydride and the phosphorus peaks were observed by ^{1}H and ^{31}P NMR together with the formation of free phosphine. The use of an internal standard allowed to quantify the amount of phosphine released to 2 (**see SI**). Moreover, the broad signal obtained by ^{1}H NMR

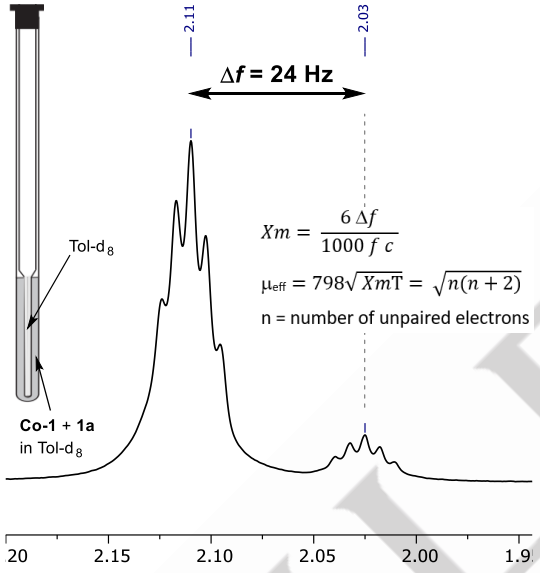
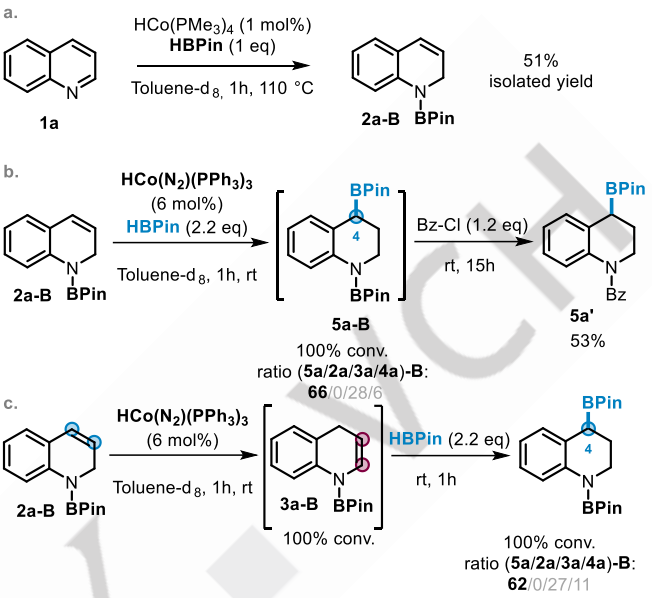


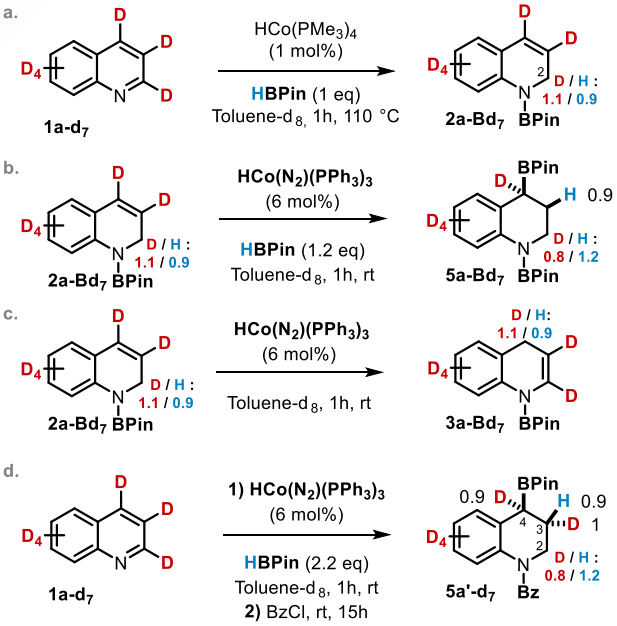
Figure 3. Evans method in toluene-d$_8$ for the measurement of the magnetic moment of the *in situ* formed paramagnetic cobalt specie

and the missing phosphine by ^{31}P NMR suggest the formation of a paramagnetic complex that we were not able to isolate. To determine the magnetic moment of this putative paramagnetic species and the number of unpaired electrons, we used the Evans method based on the difference of the NMR chemical shift of the solvent.[24] The effective magnetic moment (μ_{exp}) of this complex was found to be 3.01, which coincides with the theoretical result (2.80) calculated for two unpaired electron characteristic of a triplet state of the cobalt. Finally, subsequent addition of 10 equivalent of HBPin onto the paramagnetic intermediate allows in 10 minutes the formation of the desired borylated tetrahydroquinoline **5a-B** (**See SI**). We then tackled the second step of the cascade. For that purpose, we synthesized the borylated 1,2-DHQ with HCo(PMe$_3$)$_4$ **Co-2** as we saw that this catalyst selectively provides **2a-B** (Entry 9, **Table 1**) which can be easily purified (**Scheme 4a**). Then using **2a-B** as the starting material of the reaction in standard conditions, a full conversion was observed leading to a mixture of the desired bis-borylated product, 1,4-DHQ and tetrahydroquinoline in a 66/0/28/6 ratio, highly similar to the one obtained in the developed optimized conditions (**Scheme 4b** vs **Scheme 2**).



Scheme 4. Mechanistic investigation of a cascade pathway

After protection with benzoyl chloride (Bz-Cl), an isolated yield of 53% was obtained for the product **5a'** (**Scheme 4b**). These results provide several information: *(i)* the two steps are indeed independent and the hypothesis of a cascade reaction is confirmed; *(ii)* as 1,4-DHQ **3a-B** is formed, it shows that the latter probably arises from an isomerization of the 1,2-DHQ **2a-B** and not from a non-selective first hydroboration of the quinoline.



Scheme 5. Isotope labelling studies

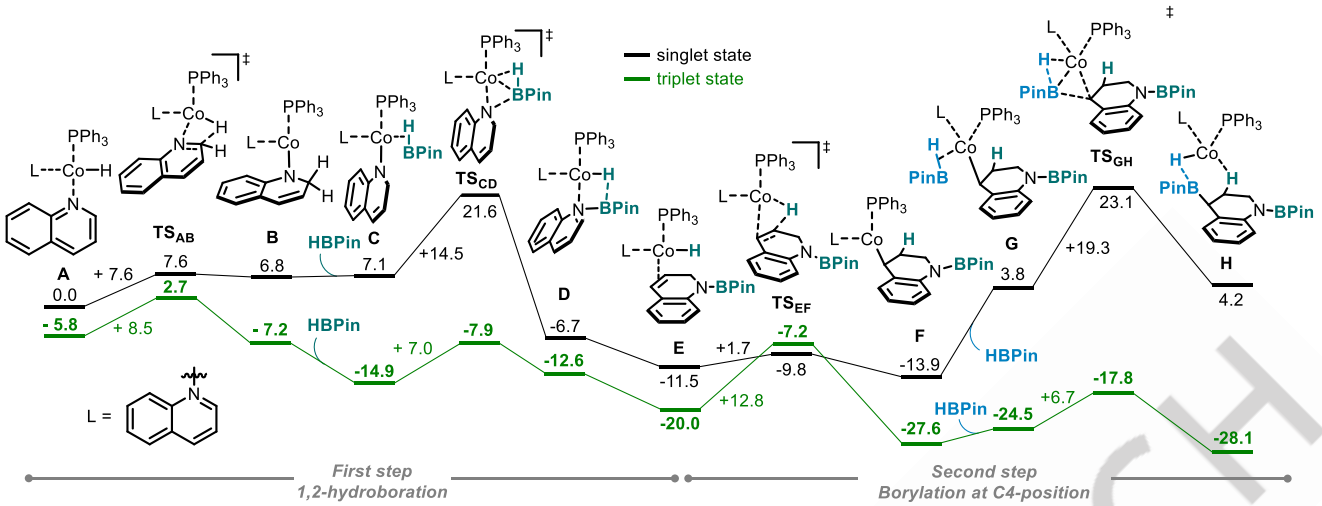


Figure 4. Gibbs free energy (in kcal.mol^{-1}) profile for the cobalt(I)-catalyzed bis-hydroboration of quinoline at the singlet and triplet states using B3LYP-D3/def2-TZVP//B3LYP-D3/ def2-SVP level of theory (CPCM: solvent = toluene).

To confirm this last point, pure **2a-B** was mixed with 6 mol% of the catalyst **Co-1**. After 1 hour at room temperature, full isomerization has occurred and only the 1,4-DHQ **3a-B** could be observed. Interestingly the borylated 1,4-DHQ **3a-B** intermediate was isomerized back into the 1,2-DHQ **2a-B** as, after addition of HBPin, **5a-B** was obtained as the major product (**Scheme 4c**). It is worth mentioning that the same reaction performed without catalyst and in presence of 2 equivalents of HBpin allows only the recovery of the 1,2-DHQ **2a-B** (**see SI**).[25] We then conducted reactions starting from the fully deuterated quinoline **1a-d$_7$**. Using $HCo(PMe_3)_4$ on quinoline **1a-d$_7$** allows the selective formation of the 1,2-DHQ **2a-Bd$_7$** with selective incorporation of hydrogen at C2 (**Scheme 5a**). Starting from the isolated **2a-Bd$_7$** the hydroboration of the double bond with $HCo(N_2)(PPh_3)_3$ was studied in presence of HBPin showing the very selective *syn*-hydroboration with the incorporation of hydrogen only at C3 (**Scheme 5b**). We then studied the 1,2- to 1,4-DHQ isomerization starting from **2a-Bd$_7$**. In the presence of $HCo(N_2)(PPh_3)_3$ without HBPin (**Scheme 5c**), a selective shift of one hydrogen/deuterium from C2 to C4 occurs without H/D scrambling at other positions (especially at C3). This experiment gives evidences for an isomerization going through highly stereospecific process, which is consistent with a hydrocobaltation/β-H elimination mechanism. Finally, treating quinoline **1a-d$_7$** in our standard conditions allows the formation of the borylated quinoline **5a'-d$_7$** after benzoylation, with the introduction of hydrogen selectively at C2 and C3 corresponding to the cascade of the two successive hydroborations (**Scheme 5d**). The slight loss of deuterium at C4 (0.9 D) may indicate that isomerization occurs to some extent before the final C–B bond is formed.

DFT Calculations. To gain a deeper insight into the mechanism and to gauge the importance of the spin states of the cobalt complexes involved, some DFT calculations at the B3LYP-D3/def2-TZVP//B3LYP-D3/def2-SVP level of theory were performed. All discussed energies are based on Gibbs free energy at 298 K and the solvent was taken into account using the CPCM solvation model (Toluene). The d^8 configuration of the cobalt(I) allows for two distinct spin states, the singlet and the triplet states. The energy associated with these states highly depends on the ligands surrounding the metal. While 18-electrons complexes are generally more stable in their singlet state, the triplet state may become favoured when fewer metal valence electrons are involved.[26] As previously mentioned, in the presence of quinoline, the $HCo(N_2)(PPh_3)_3$ evolves almost instantaneously in the reaction conditions (large excess of quinoline *vs* catalyst) toward the formation of a paramagnetic complex with the concomitant loss of two triphenylphosphine ligands (and nitrogen gas). Therefore, complex **A**, bearing one phosphine and two quinolines seems to be a suitable candidate for this resulting complex. Interestingly, the computed structure of **A** does indicate a preference for the triplet state by almost 6 kcal.mol^{-1}. From complex **A**, a reaction pathway for the bis-borylation was found and the corresponding energy profile for both spin states is depicted in **Figure 4**. The mechanism starts with the 1,2-reduction of one quinoline ligand through hydrocobaltation leading to the cobalt(I) amido complex **B** via a transition state **TS$_{AB}$** lying at about 8 kcal.mol^{-1}. In contrast to the endergonicity found for this dearomatization step in the singlet state, the process becomes slightly exergonic in the triplet state.

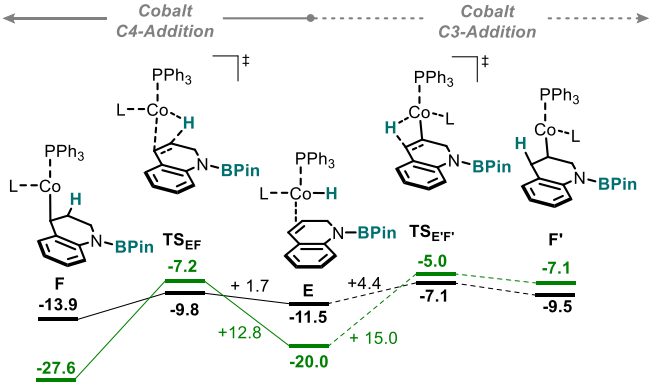
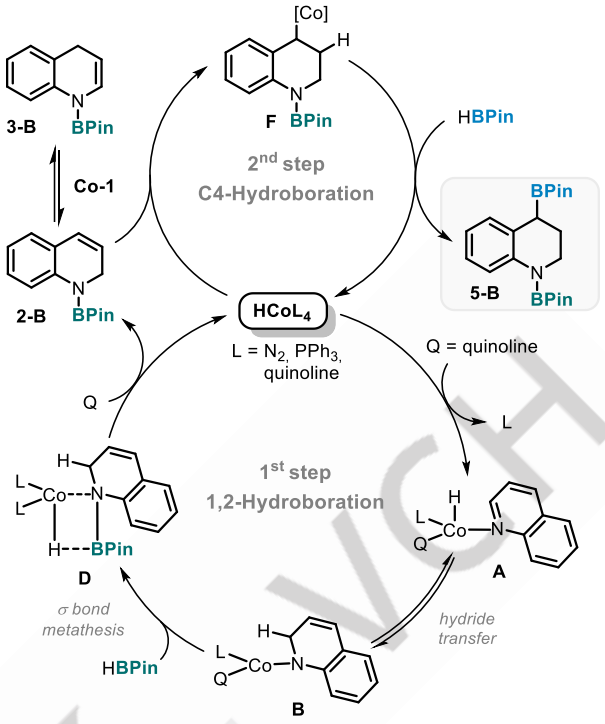


Figure 5. DFT calculations for the second hydrocobaltation step at the singlet and triplet states. Comparison to form **F** and **F'** regioisomers from the same intermediate **E**.

Interestingly, the intermediate **B** features a pseudo-agostic bond that is not present for the high spin state. The addition of a pinalcolborane molecule to **B** resulted in the formation of the σ-borane complex **C**, which is energetically much favored in the triplet state. From the complex **C**, a transition state $\mathbf{TS_{CD}}$ to form the N–B bond of compound **2a-B**, akin to a σ-complex assisted metathesis,[27] could be calculated with a low activation barrier of 7.0 kcal.mol^{-1}. In contrast, to perform this metathesis step in the singlet state, twice this energy is required. Dissociation of compound **2a-B** from intermediate **D**, followed by its π-recomplexation, leads to the η^2-complex **E**. This formal isomerization sequence is thermodynamically favored for both spin states but the intermediate **E** is more stable in the triplet state by 8.5 kcal.mol^{-1}. Then, a regioselective hydrocobaltation of the internal alkene of **2a-B** to form the organocobalt intermediate **F** occurs. Although the activation energy to reach $\mathbf{TS_{EF}}$ is higher in the triplet state (12.8 vs 1.7 kcal.mol^{-1}) this step is more exergonic (-7.6 vs -2.4 kcal.mol^{-1}). The final step involves another σ-bond metathesis, between the H–B bond of pinacol borane and the Co–C bond of intermediate **F**, via the formation of σ-complex **G** and the transition state $\mathbf{TS_{GH}}$. Once again, the triplet state is favored by far from a kinetic and thermodynamic point of view. Ligand exchange on the final intermediate **H** with a quinoline molecule regenerates the starting complex **A** and releases the bis-borylated product **5a-B**. The excellent regioselectivity observed experimentally for the second hydroboration could be computationally rationalized. Indeed, the regioisomeric hydrocobaltation that would lead to an *anti*-Markovnikov hydroboration final product was found to be endergonic for both spin states and the transition states are lying at higher levels (**Figure 5**). In the triplet state, the organocobalt(I) species **F'** is about 20 kcal.mol^{-1} less stable than its regioisomer **F**. As previously seen in **Scheme 4**, without HBPin, the intermediate 1,2-DHQ **2a-B** is rapidly transformed into thermodynamically more stable 1,4-DHQ product **3a-B** when confronted to a catalytic amount of the H–Co(I) complex. Subsequential addition of HBPin to the mixture led only to the bis-borylated product **5a-B.** These experiments point out that a rapid equilibrium between DHQ isomers **2a-B** and **3a-B** operates, presumably through hydrocobaltation/β-H elimination sequences. Eventually, HBPin reacts preferentially with organocobalt(I) species **F**, which is by far the most stable and therefore the most present intermediate in the medium. To summarize the mechanism (**Scheme 6**), after two ligand exchanges with quinolines the putative paramagnetic specie **A** is formed and undergoes an intramolecular hydride transfer to generate **B** which after a σ-bond metathesis generates **D**. The latter can either release the *N*-borylated 1,2-DHQ **2-B** together with the cobalt hydride, or enter directly in the C4-hydroboration cycle in which the intermediate **F** with the cobalt at C4 is preferentially formed. A second σ-bond metathesis allows then the formation of the 1,4-bis-borylated THQ **5-B**.



Scheme 6. Proposed mechanism

Conclusion

In conclusion, we developed mild and efficient conditions for the selective one-pot dearomatization and functionalization of quinolines towards 1,4-bis-borylated tetrahydroquinolines in 1h at room temperature. A two-steps cascade was proposed, starting from a paramagnetic bis-quinoline cobalt hydride complex, and was confirmed by means of NMR spectroscopy analysis and deuteration studies. X-ray diffraction of several adducts confirmed the observed regio- and stereoselectivity. Finally, DFT calculations rationalized both the reactivity and the regioselectivity, and shed light on the importance of the cobalt triplet state all along the process. The latter being also evidenced using the Evans NMR method. This work paves the way to tandem *N*-heteroarene reduction/functionalization using non-noble metals.

Experimental Section

Commercial reagents and solvents were purchased from Sigma-Aldrich, TCI, Fisher Scientific or Fluorochem and used as received without further purification. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporatory. Chromatographic purifications of products were accomplished using force-flow chromatography on Macherey-Nagel SI 60 Å (40 – 63 µm) silica gel. Thin layer chromatography (TLC) was performed on Macherey-Nagel Pre-coated ALUGRAM Xtra SIL G/UV254 silica gel plates. TLC visualization was performed by fluorescence quenching (λ = 254 nm), dipping in $KMnO_4$ or paranisaldehyde stains. Filtrations through Celite® were performed using Hyflo-Supercel from VWR. ^{1}H NMR spectra

were recorded on a Brucker 600; 400 AVANCE or 300 AVANCE (600, 400 and 300 MHz respectively) and are referenced relative to residual $CHCl_3$ protons signals at δ 7.26 ppm and C_6H_5-CH_3 signals at 2.09 ppm. ^{13}C NMR spectra were recorded on a Brucker 400 AVANCE or 300 AVANCE (100 and 75 MHz respectively) and are referenced relative to $CDCl_3$ at δ 77.16 ppm. ^{31}P spectra were recorded on a Brucker 600 and 400 AVANCE (243 and 162 MHz respectively). Data are reported as follows: chemical shift (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, s = septuplet, m = multiplet, bs = broad signal, app. = apparent), coupling constant (Hz) and integration. High-resolution Mass spectra were obtained from the Laboratoire Chimie Structurale Organique et Biologique (Sorbonne Université) and performed on a LTQ Orbitrap Thermo Scientific (ESI, APCI). DRX spectrum and resolution were performed on a Bruker AXS Kappa-APEX II. Catalysts **Co-1**, **Co-2**, and **Co-3** have been synthetized according to the literature.[18c, 28,29]

General procedure A for the Bis-Hydroboration cascade of quinolines using Co-1

In the glovebox under argon, was introduced in a microwave vial $HCo(N_2)(PPh_3)_3$ **Co-1** (26.2 mg, 0.03 mmol, 6 mol%). Were added by micro-syringes pinacolborane HBPin (160 µL, 1.1 mmol, 2.2 eq), Toluene-d_8 (100 µL) and quinoline (0.5 mmol, 1 eq). The microwave vial was sealed. All the liquids were degassed separately before addition via purging with argon for a period of 15 min. After stirring at room temperature for 1h, an aliquot of the mixture was collected and diluted with Toluene-d_8 (0.4 mL) in a J. Young NMR tube and analysed in ^1H NMR spectroscopy in order to determine the conversion of the reaction and the ratio of the products.

General procedure B for the protection of the bis-borylated tetrahydroquinolines

Into the microwave vial of the crude material, were then added under argon at room temperature the acyl chloride (0.6 mmol, 1.2 eq) and the aliquots previously diluted with Toluene-d_8 for the ^1H NMR analysis. After stirring for 15h at room temperature, the reaction was filtered through a plug of silica/Celite® and washed with DCM/AcOEt. The crude material was finally purified by flash column chromatography over silica gel.

(4-nitrophenyl)(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-1(2H)-yl)methanone (5a)

According to General procedures **A** and **B**. Silica gel flash chromatography (eluent petroleum ether/ethyl acetate: 90/10). Crystals have been obtained by diffusion of pentane through CH_2Cl_2. Yellow solid (147 mg, 72% yield). **^1H NMR** (600 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 2H, ArH), 7.66 (d, J = 8.5 Hz, 2H, ArH), 7.19 (dd, J = 7.6, 1.5 Hz, 1H, ArH), 7.02 (td, J = 7.6, 1.2 Hz, 1H, ArH), 6.78 (t, J = 7.6 Hz, 1H, ArH), 6.38 (bs, 1H, ArH), 4.25 (bq, J = 9.7 Hz, 1H, CH_2), 3.62 (ddd, J = 12.3, 7.0, 4.1 Hz, 1H, CH_2), 2.66 (t, J = 5.1 Hz, 1H, CH), 2.44-2.38 (m, 1H, CH_2), 1.96 (dddd, J = 12.9, 9.5, 7.0, 5.8 Hz, 1H, CH_2), 1.22 (s, 6H, CH_3), 1.20 (s, 6H, CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.9, 148.5, 142.5, 137.9, 136.0, 130.3 (2C), 128.2, 126.0, 125.7, 125.5, 123.2 (2C), 84.3 (2C), 44.4, 26.5, 25.2 (2C), 24.7 (2C), 24.3. **$^{11}B\{^1H\}$ NMR** (128 MHz, $CDCl_3$) δ 33.8. **HRMS** (ESI) *m/z*: [M+H]+ Calculated for $C_{22}H_{25}BN_2O_5H$ 409.1929; Found 409.1933.

Acknowledgements

We warmly thank Gilles Clodic (Sorbonne Université) for HRMS analyses and Sébastien Blanchard for fruitful discussion on magnetism. This work was granted access to the HPC resources of the SACADO MeSU platform at Sorbonne Université. This work was supported by CNRS, MRES, and Sorbonne Université, which we gratefully acknowledge.

Data Availability Statement

The data that support the findings of this study are available in the supporting information of this article. The authors have cited additional references within the supporting information.[28-30]

Keywords: cobalt • triplet state • hydroboration • *N*-heteroarene• DFT calculation

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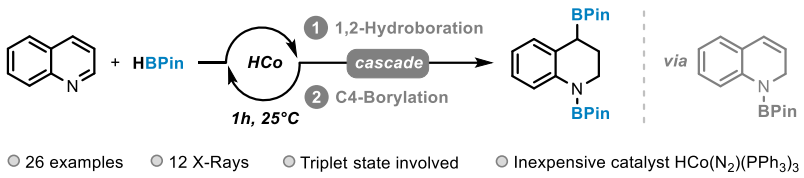

○ 26 examples ○ 12 X-Rays ○ Triplet state involved ○ Inexpensive catalyst $HCo(N_2)(PPh_3)_3$

Selective tandem quinolines dearomatization/functionalization is a huge challenge. We show here that the low-valent $HCo(N_2)(PPh_3)_3$ is able to catalyze such bis-borylation process. NMR and labelling studies prove a 1,2-hydroboration/Markovnikov hydroboration cascade, starting from an *in situ* formed paramagnetic complex. DFT highlights the importance of a cobalt triplet state throughout the reaction, and bring rationalizations on the C4 selectivity.

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