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COBALT-CATALYZED C5-SELECTIVE C-H FUNCTIONALIZATION OF 4-Me-QUINOLINES WITH STYRENES: AN APPROACH TO 5,6-DIHYDRO-4H-BENZO[de]QUINOLINES

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This paper is dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday.

Abstract – Cobalt-catalyzed C5-selective C-H functionalization of 4-Me-quinolines is described. A postulated cobalt-hydride catalyst, generated from 2 mol % of CoI₂, promoted the reaction of 4-Me-quinolines with styrenes, giving 5,6-dihydro-4H-benzo[de]quinolines (34-55% yield) in one-pot. A plausible reaction mechanism is also described.

Nitrogen-containing heteroarenes are important structural cores found in many biologically active natural products, drug candidates, and clinically applied drugs.¹ In medicinal chemistry research, modifications of heteroarenes are often necessary to optimize the properties of drug candidates. For example, in lead optimization studies of the pentacyclic anti-cancer camptothecin, a quinoline core was intensively modified (Figure 1).² Hexacyclic camptothecin analogs bearing the 5,6-dihydro-4H-benzo[de]quinoline core had high topoisomerase I inhibitory activity,^{2a,2b} and exatecan (DX8951f) mesylate is now clinically used as a water-soluble camptothecin analog.^{2c} Previous methods for synthesizing the 5,6-dihydro-4H-benzo[de]quinoline core, however, often required multi-step processes including quinoline construction.^{2,3} Thus, studies are needed for the development of a concise straightforward approach starting from readily available quinolines.

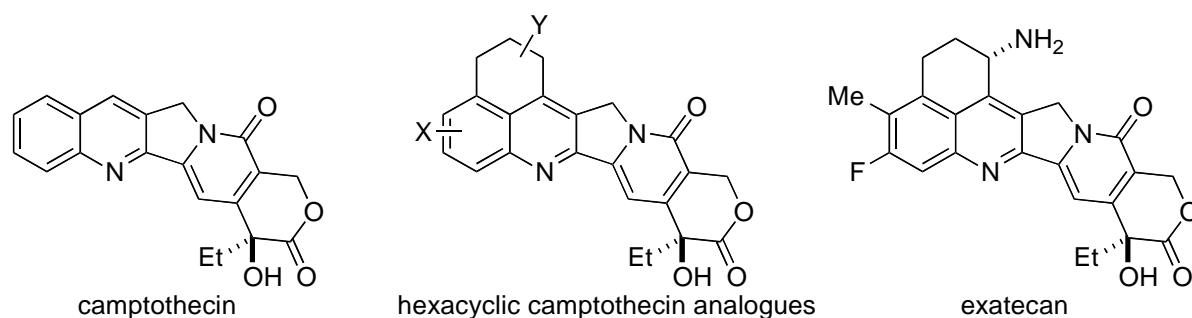
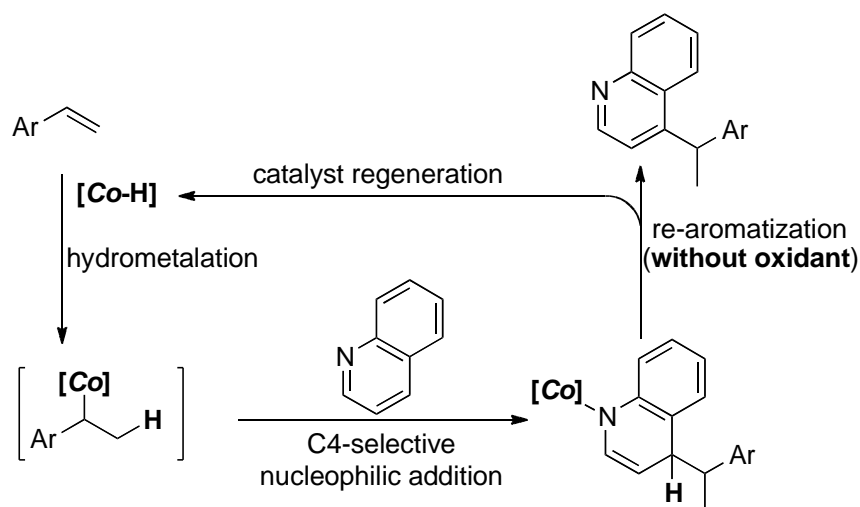


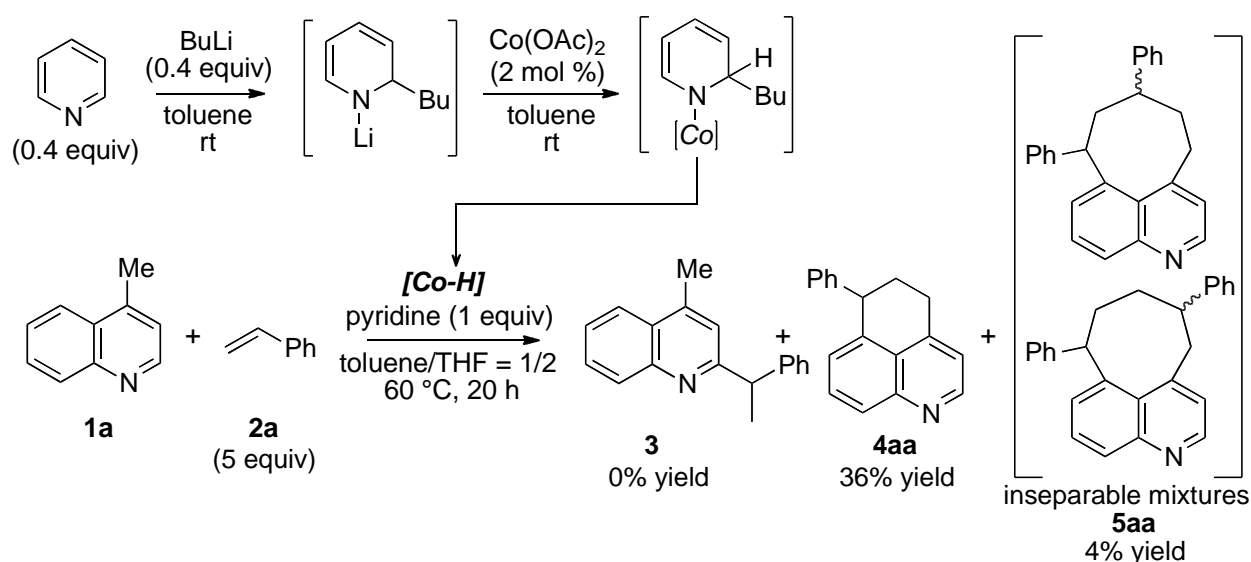
Figure 1. Structures of camptothecin, its hexacyclic analogues bearing a 5,6-dihydro-4*H*-benzo[*de*]-quinoline core, and exatecan

Transition metal-catalyzed regioselective direct C-H bond functionalization of heteroarenes has attracted attention because it provides rapid access to various functionalized heteroarenes.⁴ In many reports, a Lewis basic sp^2 nitrogen atom in the heteroarenes is used as a directing group to achieve C2-selective C-H bond functionalization of pyridines and quinolines.⁵ In contrast, methods for selectively functionalizing other positions are rare. Recently, several groups reported either C3-,⁶ C4-,⁷ or C8-selective⁸ catalytic C-H functionalization of pyridines and quinolines. As a part of our ongoing studies of first-row transition metal-catalyzed C-H functionalization,⁹⁻¹² we also succeeded in C4-selective alkylation of pyridines^{10a} and quinolines.^{10b} Our approach, utilizing a postulated cobalt-hydride species generated from cobalt amide, is summarized in Scheme 1. Mechanistic studies suggested that the reaction proceeds via hydrometalation/C4-selective nucleophilic addition/re-aromatization,^{13,14} giving C4-alkylated pyridines and quinolines with no stoichiometric oxidant. Here we describe further application of our cobalt catalysis for C5-selective C-H functionalization of 4-Me-quinolines with styrenes, giving 5,6-dihydro-4*H*-benzo[*de*]quinolines in one-pot.

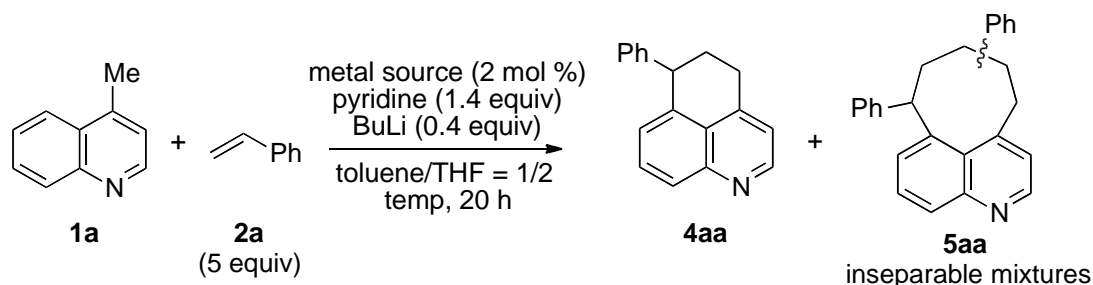


Scheme 1. Postulated mechanism of C4-selective alkylation of quinolines under cobalt catalysis

As a part of the mechanistic studies of C4-selective alkylation of quinolines, we investigated the reaction with 4-Me-quinoline, expecting that alkylation would proceed at the C2-position. Unexpectedly, however, the reaction of 4-Me-quinoline with styrene under the optimized conditions for C4-alkylation of quinolines [2 mol % of $\text{Co}(\text{OAc})_2$, 0.4 equiv of BuLi, 1.4 equiv of pyridine, Scheme 2]^{10b} gave C5-functionalized 5,6-dihydro-4*H*-benzo[*de*]quinoline **4aa** in 36% yield (determined by ^1H NMR with an internal standard), while C2-alkylated product **3** was not obtained. Products **5aa** with a 5,6,7,8-tetrahydro-4*H*-cycloocta[*de*]quinoline core, derived from 4-Me-quinoline and two equivalents of styrene, were also obtained in 4% yield as inseparable regio- and diastereo-mixtures. Because there are no reports of transition metal-catalyzed C5-selective C-H functionalization of quinolines,¹⁵ we further optimized the reaction conditions to improve the yield of C5-functionalized products (Table 1). Among the reaction parameters,¹⁶ metal sources significantly affected the yield of the desired C5-functionalized products, and $\text{Co}(\text{OAc})_2$ produced a much better yield than the other metal acetates (entry 1 vs entries 2-6). The cobalt salt counter ion was also important (entries 7-10), and CoI_2 was the best, giving **4aa** in 61% NMR yield together with 22% of **5aa** (entry 10). Finally, the reaction at 70 °C with CoI_2 was selected as the best conditions, giving 62% of **4aa** (55% isolated yield) and 26% of **5aa** (entry 11). Although any explanation is too speculative at the moment, we assume that the active species of the present reaction with excess hydride sources (0.4 equiv) over cobalt salts (2 mol %) would be a cobalate species, which could explain why the cobalt salt counter ion impacted the reactivity.



Scheme 2. Unexpected formation of 5,6-dihydro-4*H*-benzo[*de*]quinoline from 4-Me-quinoline

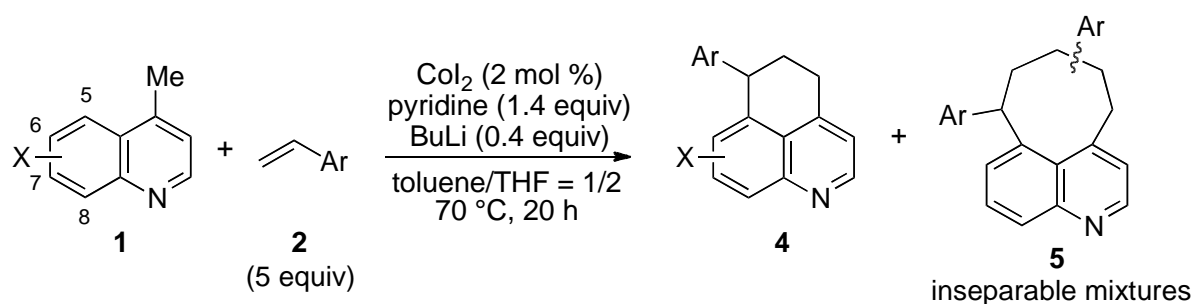
Table 1. Optimization Studies for 5,6-Dihydro-4*H*-benzo[*de*]quinoline Synthesis

entry	metal source	temp (°C)	% yield of 4aa ^a	% yield of 5aa ^a
1	Co(OAc) ₂	60	36	4
2	CuOAc	60	5	0
3	Cu(OAc) ₂	60	4	1
4	Mn(OAc) ₂	60	4	2
5	Fe(OAc) ₂	60	7	3
6	none	60	5	0
7	CoF ₂	60	22	14
8	CoCl ₂	60	36	7
9	CoBr ₂	60	54	15
10	CoI ₂	60	61	22
11	CoI ₂	70	62 (55) ^b	26 (26) ^b

Footnote ^a Determined by ¹H NMR analysis of crude mixture with dibromoethane as an internal standard.

^b Number in parenthesis is the isolated yield after purification by silica gel column chromatography.

The preliminary substrate scope of the reaction under the optimized conditions is shown in Table 2. The reaction of 4-Me-quinoline **1a** with various styrene derivatives **2a-2e** proceeded to give the desired products **4aa-4ae** in 35-55% yield (entries 1-5). The scope of quinolines, however, was narrow, and subtle changes in the substituent on the quinoline ring prevented the desired reaction. 4,7-Me₂-quinoline **1b** gave **4ba** in 34% yield (entry 6), while a substituent at the C6-position significantly retarded the desired C5-functionalization (entries 7-8). Further trials to improve the reactivity and broaden the scope of quinolines by modifying the cobalt catalyst are ongoing.

Table 2. Cobalt-Catalyzed 5,6-Dihydro-4*H*-benzo[*de*]quinoline Synthesis from 4-Me-Quinolines and Styrenes

entry	X: 1	Ar: 2	4	% yield of 4 ^a	5	% yield of 5 ^a
1	H, 1a	Ph, 2a	4aa	55	5aa	26
2	H, 1a	2-Me-C ₆ H ₄ , 2b	4ab	47	5ab	36
3	H, 1a	3-Me-C ₆ H ₄ , 2c	4ac	51	5ac	19
4	H, 1a	4-Me-C ₆ H ₄ , 2d	4ad	35	5ad	trace
5	H, 1a	3-MeO-C ₆ H ₄ , 2e	4ae	49	5ae	40
6	7-Me, 1b	Ph, 2a	4ba	34	5ba	trace
7	6-Me, 1c	Ph, 2a	4ca	9 ^b	5ca	0
8	6-MeO, 1d	Ph, 2a	4da	0 ^b	5da	0

Footnote ^a Isolated yield after purification by silica gel column chromatography. Yield of **5** is the combined yield of inseparable regio- and diastereoisomers. ^b Determined by ¹H NMR analysis of crude mixture with dibromoethane as an internal standard.

The hypothetical catalytic cycle of the reaction is shown in Figure 2. Based on previous reports on the reactivity of 4-Me-pyridines,¹⁷ we speculate that a relatively acidic benzylic position would be deprotonated with a basic cobalt-hydride species (or excess lithium amide generated from pyridine and BuLi) to give a Co-amide intermediate **I**. Addition of **I** to styrene **2** would afford a key organo-cobalt intermediate **II**. Because the C5-position of the quinoline unit is electrophilic, intramolecular nucleophilic addition of the organo-cobalt species¹⁸ onto the quinoline ring would proceed to give **III** by analogy with our previous reports on C4-alkylation of pyridines^{10a} and quinolines.^{10b} We assume that the C5-selective addition to the quinoline ring was difficult with C6-substituted substrates due to steric hindrance (Table 2, entries 7-8). Re-aromatization of the quinoline ring via cobalt-hydride elimination would afford **4** and regenerate the cobalt-hydride species. Studies to gain insight into the reaction mechanism are ongoing in our group.

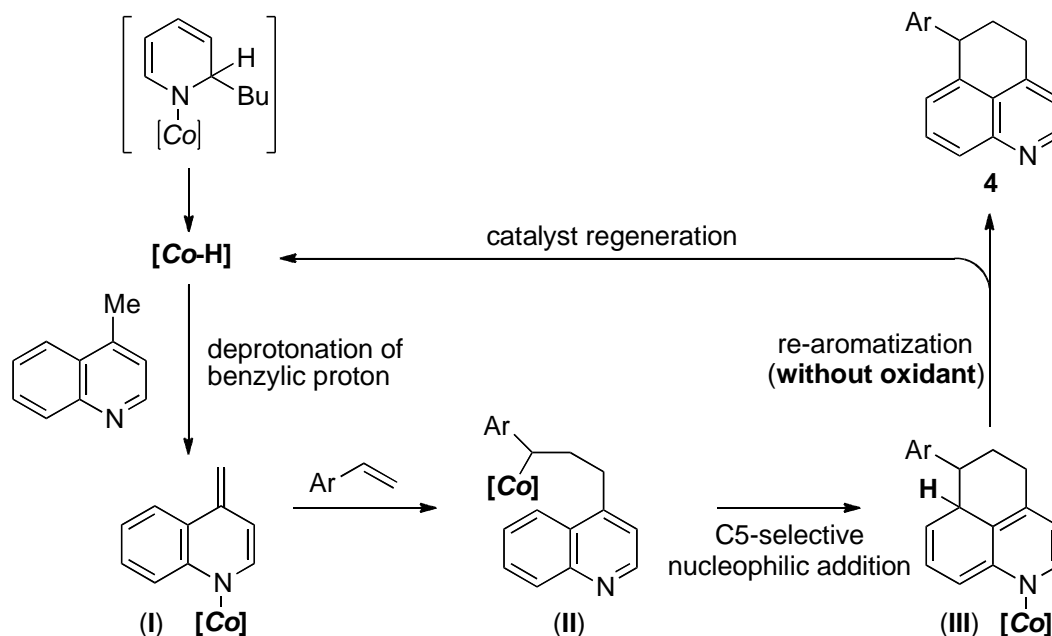


Figure 2. Hypothetical catalytic cycle

In summary, we developed a cobalt-catalyzed C5-selective C-H functionalization of 4-Me-quinolines. A postulated cobalt-hydride catalyst, generated from 2 mol % of CoI₂, promoted the reaction of 4-Me-quinolines with styrenes, giving 5,6-dihydro-4*H*-benzo[*de*]quinolines in 34-55% yield. Although the scope of 4-Me-quinolines is narrow, the present method provides a new straightforward approach to construct a useful 5,6-dihydro-4*H*-benzo[*de*]quinoline core.

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