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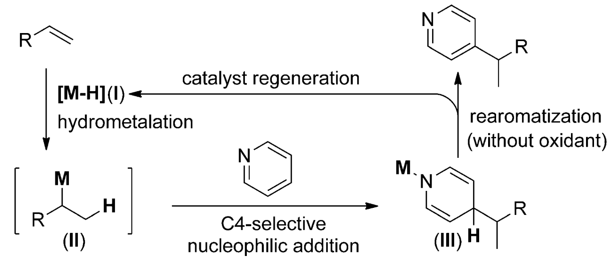
Regioselective Catalysis

Cobalt-Catalyzed C4-Selective Direct Alkylation of Pyridines**

Takashi Andou, Yutaka Saga, Hirotomo Komai, Shigeki Matsunaga,* and Motomu Kanai*

A pyridine core is a ubiquitous structural motif found in many biologically active natural products and pharmaceuticals. The regioselective functionalization of pyridines,[1] such as the C2-selective addition of highly reactive nucleophiles and C2-selective deprotonation with a strong base followed by reactions with electrophiles,[2] has long been investigated by many researchers. Catalytic C–H bond functionalization of pyridines provides atom-[3] and step-economical[4] methods for accessing various functionalized pyridines, and thus has attracted recent interest.[5–16] In many reports, a Lewis basic sp^2 nitrogen atom in the pyridine ring was utilized as the directing group, and C–H bond activation by transition-metal catalysts occurred selectively at the C2 position.[5,7] In contrast, reports on the C3- or C4-selective catalytic C–H bond functionalization of pyridines without an additional directing group are limited.[8–11] Thus, further studies into the development of new catalysts for C3- or C4-selective direct functionalization of pyridines are highly desirable. In 2010, Nakao, Hiyama, and co-workers,[10a] and Ong et al.[10b] independently reported the first C4-selective direct functionalization of pyridines through an oxidative addition/insertion/reductive elimination sequence catalyzed by Ni^0 and bulky Lewis acids. There remains room for improvement in the C4-selective direct functionalization of pyridines, however, especially in terms of catalyst loading.

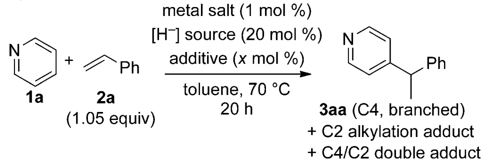
To realize the C4-selective alkylation of pyridines, we searched for a new catalyst system based on a different strategy, catalytic nucleophilic addition/rearomatization.[14–16] Our working hypothesis is shown in Scheme 1. Hydrometalation of alkenes with a metal hydride catalyst (**I**) would afford an alkyl–metal species (**II**). If the alkyl–metal species (**II**) has sufficient nucleophilicity, its addition to pyridine may afford a dihydropyridine intermediate (**III**). To realize an atom-economical catalytic process, rearomatization of pyridine without any oxidants and regeneration of the metal-hydride catalyst (**I**) are required.



Scheme 1. Working hypothesis for the atom-economic catalytic C4-selective alkylation of pyridines.

We first screened various metal salts and hydride sources that fulfilled the requirements for Scheme 1. Selected results from the optimization studies are summarized in Table 1.

Table 1: Optimization studies.



Entry	Metal	Additive (x mol%)	[H$^-$]	Yield [%][a]	Product ratio[b] (C4/C2/double)
1	FeBr$_2$	none	LiBEt$_3$H	10	>20:1:0
2	NiBr$_2$	none	LiBEt$_3$H	24	>20:1:0
3	MnBr$_2$	none	LiBEt$_3$H	22	>20:1:0
4	CuBr	none	LiBEt$_3$H	3	>20:1:0
5	CoBr$_2$	none	LiBEt$_3$H	77	1.8:1:0.2
6	CoBr$_2$	none	NaBEt$_3$H	10	1.3:1:0
7	CoBr$_2$	none	KBEt$_3$H	2	>20:1:0
8	CoBr$_2$	none	DIBAL-H	2	0:1.3:1
9	CoBr$_2$	none	none	0	–
10	none	none	LiBEt$_3$H	4	>20:1:0
11	CoBr$_2$	PCy$_3$ (3)	LiBEt$_3$H	77	1.3:1:0
12	CoBr$_2$	IMes (3)	LiBEt$_3$H	34	2.5:0:1
13	CoBr$_2$	Et$_3$B (20)	LiBEt$_3$H	95[c]	7.0:1:0.52
14	CoCl$_2$	Et$_3$B (20)	LiBEt$_3$H	82	6.7:1:0.25
15	Co(acac)$_2$	Et$_3$B (20)	LiBEt$_3$H	88	7.4:1:0.26
16	CoBr$_2$	Et$_3$B (20) +HMPA (30)	LiBEt$_3$H	91[c]	>20:1:0.38

[a] Combined yield of alkylated products based on pyridine **1a**. Determined by ^{1}H NMR analysis of the crude mixture using 1,2-dibromoethane as an internal standard. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Combined yield of alkylated products after purification by silica gel column chromatography. acac = acetylacetonate, Cy = cyclohexyl, DIBAL-H = diisobutylaluminum hydride, HMPA = hexamethylphosphoramide, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

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[*] Dr. T. Andou,[+] Y. Saga,[+] H. Komai, Dr. S. Matsunaga, Prof. Dr. M. Kanai
Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: smatsuna@mol.f.u-tokyo.ac.jp
kanai@mol.f.u-tokyo.ac.jp

Y. Saga,[+] H. Komai, Prof. Dr. M. Kanai
JST, ERATO, Kanai Life Science Catalysis Project
Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

Dr. S. Matsunaga
JST, ACT-C, Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

[+] These authors contributed equally to this work.

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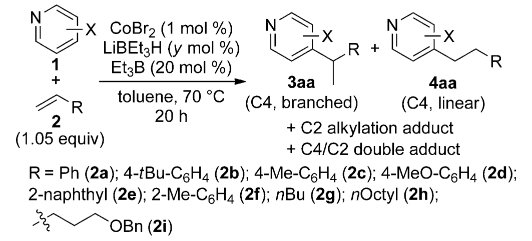
Catalytic amounts of Fe, Ni, Mn, and Cu salts in the presence of $LiBEt_3H$ (20 mol%) resulted in unsatisfactory yields (entries 1–4). In contrast, $CoBr_2$ (1 mol%) promoted the reaction of pyridine **1a** with styrene **2a**, affording alkylation product **3aa** in 77% yield and with a branched/linear selectivity of >20:1, but low C4/C2 selectivity (1.8:1; entry 5). We also screened other hydride sources (entries 6–8), but $LiBEt_3H$ was crucial for obtaining product **3aa** in good yield. Control experiments using either $CoBr_2$ alone (entry 9) or $LiBEt_3H$ alone (entry 10) gave poor results. Thus, the combination of $CoBr_2$ and $LiBEt_3H$ was important for obtaining high reactivity. To improve C4/C2 selectivity, we investigated ligands such as phosphines and N-heterocyclic carbenes, but observed no improvement (entries 11 and 12). On the other hand, the addition of Et_3B effectively improved C4/C2 selectivity, and the alkylation adduct was obtained in 95% yield, and with branched/linear = >20:1 and C4/C2 = 7.0:1 selectivities (entry 13). Other cobalt salts, such as $CoCl_2$ and $[Co(acac)_2]$ (acac = acetylacetonate) gave comparable C4/C2 selectivity (entries 14 and 15), but the reactivity was slightly lower than with $CoBr_2$. Hexamethylphosphoramide (HMPA; 30 mol%) in combination with Et_3B further improved the C4/C2 selectivity to >20:1 (entry 16).[17]

The substrate scope of the C4-selective direct pyridine alkylation is summarized in Table 2. The reaction of pyridine and its derivatives **1a**–**1d** with styrene derivatives **2a**–**2f** (1.05 equiv) proceeded smoothly when using $CoBr_2$ (1 mol%), $LiBEt_3H$ (20–30 mol%), and Et_3B (20 mol%). Good to high branched selectivity (>20:1–7.4:1) and C4 selectivity (>20:1 for all entries)[18] were observed for entries 1–5 and 9–17. Aliphatic 1-alkenes **2g**, **2h**, and **2i** were also applicable, but the reactivity of **2g**–**2i** was much lower than that of the styrene derivatives. An increase in the loading of $CoBr_2$ (6 or 9 mol%) and $LiBEt_3H$ (200 or 300 mol%) and the use of excess aliphatic alkenes were required to promote alkylation. As shown in entries 6–8, linear products **4ag**–**4ai** (branched/linear = 1:>20) were obtained in 58–86% yield with high C4 selectivity (>20:1).[19] When using bipyridine **1e**, a product doubly alkylated at the C4 and C4' positions was obtained in 85% yield by performing the reaction with styrene (5.0 mol equiv; entry 18). Notably, the reaction of 3-picoline **1b** with styrene **2a** proceeded smoothly on a gram scale with as little as 0.025 mol% of $CoBr_2$, which equates to a substrate/catalyst (s/c) ratio of 4000 (Scheme 2). The high turnover number (TON; 3440) of the reaction is also noteworthy.

To obtain preliminary insights into the reaction mechanism, we performed control experiments (Schemes 3–5). First, to assess the catalyst turnover process, the reaction was performed starting from a cobalt amide species **5** (a model for **III** in Scheme 1), which was generated by the procedure shown in Scheme 3. Pyridine (0.2 equiv) was first reacted with PhLi (0.2 equiv), and $CoBr_2$ (1 mol%) was added to the mixture to generate proposed cobalt amide **5**. An active cobalt–hydride species [Co–H] would then be generated from **5** by β-hydride elimination. With the presumed cobalt hydride catalyst generated in situ in the absence of $LiBEt_3H$ and Et_3B, the alkylation of pyridine indeed proceeded to give **3aa** in 70% yield.[20] The observed C4/C2 selectivity was similar to that in Table 1, entry 5, thus supporting the intermediacy and regeneration of the cobalt–hydride species[21] in the actual catalytic cycle of the reactions in Table 2.

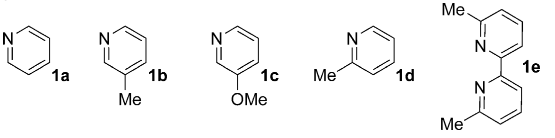
Table 2: Cobalt-catalyzed direct C4-selective alkylation of pyridines with alkenes.[a]

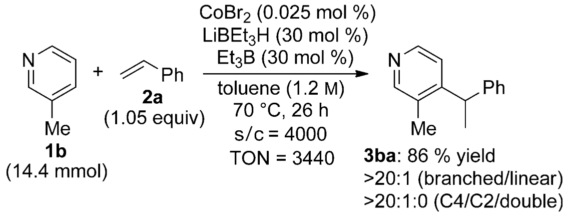


R = Ph (**2a**); 4-*t*Bu-C_6H_4 (**2b**); 4-Me-C_6H_4 (**2c**); 4-MeO-C_6H_4 (**2d**); 2-naphthyl (**2e**); 2-Me-C_6H_4 (**2f**); *n*Bu (**2g**); *n*Octyl (**2h**);

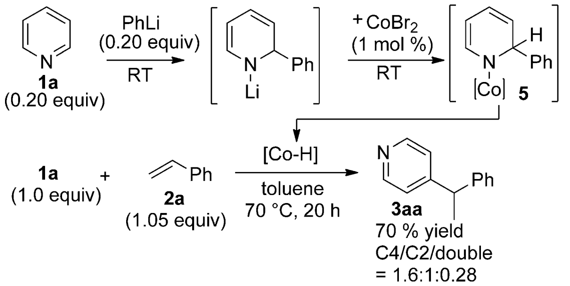
Entry	1	$LiBEt_3H$ [mol%]	2	Yield [%][b]	3,4	Branched/linear product ratio[c]	C4/C2/double product ratio[c]
1[d]	**1a**	20	**2a**	91	**3aa**	>20:1	>20:1:0.38
2[d]	**1a**	30	**2b**	87	**3ab**	>20:1	>20:1:1.1
3	**1a**	30	**2c**	83	**3ac**	>20:1	>20:1:trace
4	**1a**	30	**2d**	77	**3ad**	>20:1	>20:1:0
5	**1a**	30	**2e**	60	**3ae**	7.4:1	>20:1:0
6[e]	**1a**	200	**2g**	71	**4ag**	1:>20	>20:1:0
7[e]	**1a**	200	**2h**	86	**4ah**	1:>20	>20:1:0
8[f]	**1a**	300	**2i**	58	**4ai**	1:>20	>20:1:0
9	**1b**	20	**2a**	89	**3ba**	>20:1	>20:1:trace
10	**1b**	20	**2b**	97	**3bb**	>20:1	>20:1:0
11	**1b**	20	**2c**	84	**3bc**	>20:1	>20:1:0
12	**1b**	20	**2f**	87	**3bf**	>20:1	>20:1:0
13	**1c**	30	**2a**	96	**3ca**	>20:1	>20:1:0
14	**1c**	30	**2b**	88	**3cb**	>20:1	>20:1:0
15	**1c**	30	**2c**	86	**3cc**	>20:1	>20:1:trace
16	**1c**	30	**2f**	81	**3cf**	>20:1	>20:1:0
17[g]	**1d**	30	**2a**	63	**3da**	>20:1	>20:1:trace
18[h]	**1e**	30	**2a**	85	**3ea**	>20:1	C4 only

[a] The reaction was run using **1** (0.90 mmol), **2** (1.05 equiv), $CoBr_2$ (1 mol%) and Et_3B (20 mol%) in toluene (0.3 M) at 70°C, unless otherwise noted. [b] Combined yield of alkylated products based on **1** after purification by silica gel column chromatography. [c] Determined by ^1H NMR analysis of the crude mixture. [d] HMPA (30 mol%) was added. [e] $CoBr_2$ (6.0 mol%) and excess alkenes (**2g**: 12 equiv, **2h**: 13.5 equiv) were used. [f] $CoBr_2$ (9.0 mol%) and excess **2i** (15.2 equiv) were used. [g] Reaction was run in the absence of Et_3B. [h] 5.0 mol equiv of **2a** was used and a product doubly alkylated at the C4 and C4′ positions was obtained.



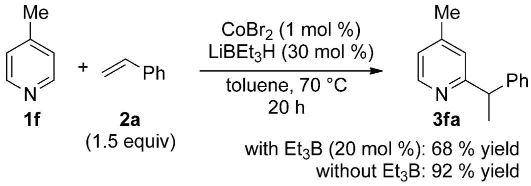


Scheme 2. Gram-scale reaction with reduced catalyst loading (s/c=4000).



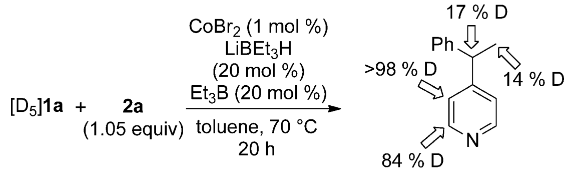
Scheme 3. In situ generation of the active cobalt species in the absence of LiBEt$_3$H and Et$_3$B.

The presence of catalytic Et$_3$B was key to improving the C4-selectivity (Table 1, entry 5 vs. entry 13).[22] To assess the possible role of Et$_3$B, reactions of 4-substituted pyridine **1f** with styrene **2a** in the presence and absence of Et$_3$B were conducted (Scheme 4). C2-alkylated product **3fa** was obtained in 68% yield in the presence of Et$_3$B, whereas the yield increased to 92% in the absence of Et$_3$B. Thus, Et$_3$B does not seem to act as a simple Lewis acid to increase the electrophilicity of pyridines, but may selectively decelerate the C2 alkylation pathway, resulting in an increase in the C4 selectivity for C4-unsubstituted pyridines.[23]



Scheme 4. Reactions of C4-substituted pyridine **1f** in the presence and absence of Et$_3$B.

Although there is no direct evidence to exclude a reaction mechanism involving oxidative addition/insertion/reductive elimination promoted by a low valent cobalt species generated in situ,[24,25] a mechanism involving hydrometalation/nucleophilic addition/rearomatization (Scheme 1) appears to be more plausible for the present reaction, based on the following observations: 1) The low-valent cobalt catalyst reported by Yoshikai et al[25a] for C−H bond functionalization by oxidative addition was not effective in the present pyridine alkylation reaction.[26] 2) The C3-alkylation adduct was not detected at all under the present conditions. C3 functionalization was, however, the major side reaction in the Ni^0/Al system used by the groups of Nakao/Hiyama and Ong,[10] which proceeds through oxidative addition. 3) Profiles of H/D scrambling when using [D$_5$]pyridine as a substrate under the present cobalt-catalyzed conditions and the Ni^0/Al system were markedly different. Under the present conditions, the H/D scrambling selectively occurred at the electrophilic C2 positions (Scheme 5), possibly through the reversible addition/elimination of a cobalt–hydride species. In contrast, under the Ni^0/Al system, which proceeds by oxidative addition, H/D scrambling occurred at both the C2 and C3 positions.[10,27] Altogether, these contrasting observations suggest that the present cobalt-catalyzed C4-selective alkylation of pyridines would proceed through a pathway that does not involve oxidative addition.



Scheme 5. H/D scrambling experiment with [D$_5$]pyridine.

In summary, we have developed a new catalyst for the atom-economical C4-selective direct alkylation of pyridines. A catalytic amount of CoBr$_2$ in combination with LiBEt$_3$H gave branched adducts from styrene derivatives, and linear adducts from aliphatic alkenes. The high catalyst turnover numbers (up to 3440; s/c = 4000) observed in the reaction with styrene are noteworthy. Further studies to expand the substrate scope to other heterocyclic compounds and to clarify the reaction mechanism in more detail are ongoing in our group.

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[17] HMPA without Et_3B was not effective, giving alkylated products with modest selectivity (87 % yield, C4/C2/double = 3.2:1:0.1).

[18] In Table 2, HMPA (30 mol %) was added only when there remained room for improvement in the C4 selectivity.

[19] The observed branched/linear selectivity difference between the styrene derivatives and aliphatic alkenes can be ascribed to the relative stability differences in the alkylcobalt intermediates (**II** in Scheme 1 vs. its linear alkylmetal counterpart). Because H/D scrambling was observed at both the α- and β-positions of styrene in Scheme 5, the hydrometallation step should be reversible, at least for styrenes. The reaction between styrenes and pyridines would proceed through the thermodynamically more stable π-conjugated benzylic–cobalt intermediate, whereas the reaction of aliphatic alkenes may proceed from the kinetically favored linear alkylcobalt intermediate. For a similar discussion, see: Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *Angew. Chem.* **2010**, *122*, 4553; *Angew. Chem. Int. Ed.* **2010**, *49*, 4451.

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[22] To avoid oxygen contamination of the reaction vial, all experiments were performed in a glove box (O_2: < 0.5 ppm). Thus, the possibility of Et_3B acting as a radical initiator is less probable.

[23] Although any proposal at the current stage is too speculative, and further studies are required to precisely clarify the role of Et_3B, we assume that Et_3B would competitively prevent the cobalt species from being coordinated by the sp^2 nitrogen atom in the pyridine ring, which may lead to undesirable C2 alkylation. Alternatively, Et_3B may form an organocobalate species, which would act as a soft nucleophile and prefer addition at the C4 position. For a discussion on soft and hard nucleophile properties affecting site selectivity in additions to pyridines, see the review in Ref. [1e]. For representative catalytic reactions through organocobalates, see: a) K. Wakabayashi, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 5374; b) W. M. Czaplik, M. Mayer, A. Jacobi von Wangelin, *Synlett* **2009**, 2931; c) Z.-H. Ding, N. Yoshikai, *Org. Lett.* **2010**, *12*, 4180.

[24] For a review on Co-catalyzed C−H activation, see: a) N. Yoshikai, *Synlett* **2011**, 1047; for a general review on Co-catalyzed cross coupling reactions, see: b) G. Cahiez, A. Moyeux, *Chem. Rev.* **2010**, *110*, 1435.

[25] a) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.* **2011**, *133*, 400; b) K. Gao, P.-S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.* **2010**, *132*, 12249; For selected recent examples of other Co-catalyzed C−H functionalization reactions, see: c) Q. Chen, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 428; d) B. Li, Z.-H. Wu, Y.-F. Gu, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 1141; *Angew. Chem. Int. Ed.* **2011**, *50*, 1109; e) W. Song, L. Ackermann, *Angew. Chem.* **2012**, *124*, 8376; *Angew. Chem. Int. Ed.* **2012**, *51*, 8251; for early examples, see the review in Ref. [24].

[26] The reaction of **1a** with **2a** at 70 °C using $CoBr_2$ (10 mol %), PCy_3 (10 mol %), and Me_3SiCH_2MgCl (80 mol %, see Ref. [25a]) did not afford **3aa**.

[27] The deuterium scrambling experiment in Ref. [10a] was performed with [D_5]pyridine and 1-tridecene, not with styrene. To precisely compare the results of deuterium scrambling experiments, we additionally performed the experiment using [D_5]pyridine and styrene under the reported Ni^0 and bulky Al Lewis acid conditions. H/D scrambling at the C3 position was also observed in the reaction with styrene (MAD = (2,6-tBu$_2$-4-Me-$C_6H_2O)_2AlMe$; IMes = 1,3-(2,4,6-trimethylphenyl)imidazoyl-2-ylidene):