

論文の内容の要旨

論文題目

A New Metal-Hydride-Based Catalysis toward C-C Bond Forming Reaction and H₂ Energy System

(メタルヒドライド活性種を基盤とした新規触媒系の開発と
炭素-炭素結合形成反応並びに水素貯蔵放出エネルギーシステムへの応用)

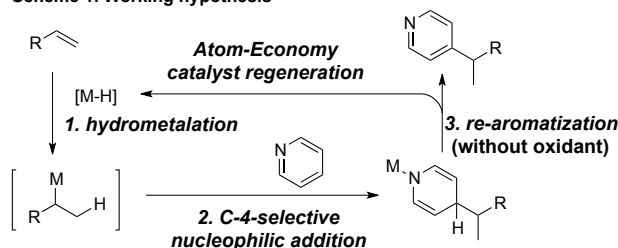
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1. Cobalt-Catalyzed C-4 Selective Direct Alkylation of Pyridines

<1-1 Background and Strategy>

Pyridine derivatives are essential motifs existing in numerous biologically active compounds, drug candidates, and useful materials. The exploration of efficient catalytic methodologies for regioselective C-H bond functionalization of pyridines thus has attracted recent interests¹. Although many researchers have achieved C2-selective C-H bond functionalization utilizing a Lewis basic sp² nitrogen atom as the directing group, there are only limited examples on C3- or C4- selective methods. Especially for C4-selective catalytic C-H bond functionalization of pyridines, Nakao/Hiyama *et al*^{2a} and Ong *et al*^{2b}, independently disclosed the first C4-selective functionalization of pyridines using Ni⁰/Lewis acid catalysis through oxidative addition/insertion/reductive elimination sequence. I envisioned that an adequate metal-hydride catalysis might realize C4-selective alkylation of pyridines *via* a completely different mechanism; 1. *hydrometalation*/2. *catalytic nucleophilic attack to pyridines*/3. *re-aromatization* (Scheme 1).

Scheme 1. Working hypothesis



<1-2 Results>

Based on the hypothesis above, I surveyed various metal salts and hydride sources. These studies revealed that the combination of CoBr₂ and LiBEt₃H was crucial for obtaining high reactivity. Further investigations identified BEt₃ as a vital additive to enhance C4/C2 selectivity. After getting the optimized conditions, I examined the substrate scope (Table 1).

The reaction of the C4-selective alkylation of pyridine derivatives **1a-1d** with styrene derivatives **2a-2f** proceeded well to afford the desired products with good to high branched selectivity (>20:1-7.4:1) and C4 selectivity (>20:1) (entries 1-5 and 9-17). Though the reactivity with aliphatic alkenes **2g, 2h**, and **2i** was much lower than aromatic alkenes, increased amount of CoBr₂ and excess amounts of LiBEt₃H and alkenes gave desired products in 58-86% yield with high C4 selectivity

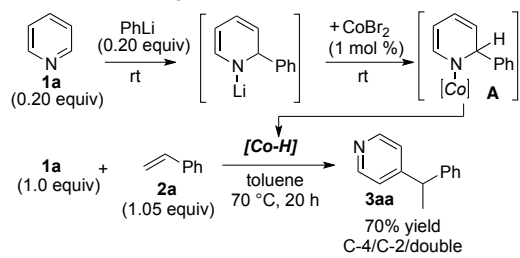
(>20:1) (entries 6-8). For aliphatic alkenes case, it was of note to obtain linear products **4ag-4ai** (branched/linear = 1: >20). The catalyst system was also applicable for bipyridine substrate **1e** to produce doubly alkylated product at C4 and C4' positions in 85% yield (entry 18).

<1-3 Mechanism Study>

To gain preliminary insight into the reaction mechanism, I carried out several investigations. First, in order to confirm catalyst regeneration process (Scheme 1, step 3), I performed the reaction starting from a postulated cobalt amide **A**, prepared by the method shown in Scheme 2. I anticipated that an active [Co-H] species would be formed from **A** through β -hydride elimination. Using the presumed [Co-H] species in the absence of BEt_3 and LiBEt_3H , I obtained alkylated product **3aa** in similar yield with similar C4-selectivity to the conditions without using BEt_3 . This observation suggests the intermediacy and regeneration of [Co-H] species in the actual catalytic cycle.

Next, I demonstrated H/D scrambling experiment with $[\text{D}_5]$ pyridine as a substrate (Scheme 3). Compared with the Ni^0/Al catalysis used by Nakao/Hiyama^{2a} and Ong^{2b}, profiles of H/D scrambling under my conditions were drastically different. Whereas under Ni^0/Al system, H/D scrambling occurred at both the C2 and C3 positions *via* oxidative addition, my conditions provoked selective H/D scrambling at the electrophilic C2 position, possibly through the reversible addition and elimination of [Co-H] species. Based on the observation, I postulated that the present C4-selective direct alkylation reaction would proceed through 1. hydrometalation/2. catalytic nucleophilic attack to pyridines/3. re-aromatization sequence³.

Scheme 2. In situ generation of the active [Co-H] species



Scheme 3. H/D scrambling experiment with $[\text{D}_5]$ pyridine

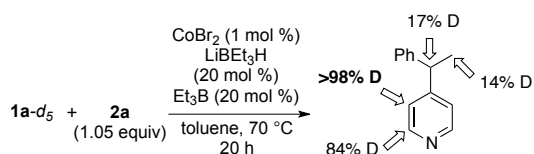
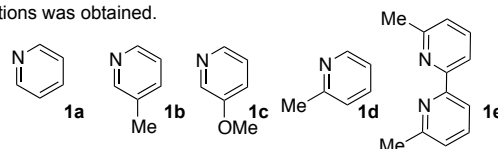


Table 1: Cobalt-catalyzed C4-selective alkylation of pyridines

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

^aHMPA (30 mol %) was added. ^b CoBr_2 (6 mol %) and excess alkenes (**2g**: 12 equiv., **2h**: 13.5 equiv.) were used. ^c CoBr_2 (9 mol %) and excess **2i** (15.2 equiv.) were used. ^dReaction was run in the absence of BEt_3 .

^e5 equiv. of **2a** was used and a doubly alkylated product at the C4 and C4' positions was obtained.



References

- (1) Nakao, Y. *Synthesis* **2011**, 3209. (2) a) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 13666. b) Tsai, C.-C.; Shih, W.-C.; Fang, C.-H.; Li, C.-Y.; Ong, T.-G.; Yap, G. P. A. *J. Am. Chem. Soc.* **2010**, *132*, 11887. (3) Andou, T.[†]; Saga, Y.[†]; Komai, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 3213. ([†]contributed equally to this work)