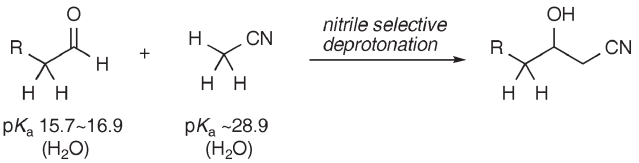
Catalytic chemoselective addition of acetonitrile to enolizable aldehydes with cationic Ru complex/DBU combination†

Naoya Kumagai, Shigeki Matsunaga and Masakatsu Shibasaki*

Received (in Cambridge, UK) 31st March 2005, Accepted 9th May 2005
First published as an Advance Article on the web 9th June 2005
DOI: 10.1039/b504519c

The cooperative catalysis of $CpRu(PPh_3)_2(CH_3CN)PF_6$ (1b) and DBU enables chemoselective nucleophilic activation of acetonitrile in the presence of base-sensitive aldehydes 2 to afford corresponding β-hydroxynitriles 3 in good yield.

The control of chemoselectivity is ongoing challenge in synthetic organic chemistry. For decades, reagent-controlled chemoselectivity has been realized using more than stoichiometric amounts of additional reagents. For example, a separate preparation process of metal-enolate or enol silyl ether enables various cross-aldol reactions,[1] while a simple base-promoted cross-aldol protocol often results in complicated product mixtures, including self-aldol products of aldehydes. Recently, attention in aldol-type reaction development has shifted to a catalyst controlled chemoselective process;[2] that is, *in situ* catalytic generation of active nucleophiles and subsequent integration into a C–C bond forming process. Although α-cyano carbanions are widely utilized in organic synthesis as useful carbon nucleophiles, the catalytic process for generating α-cyano carbanions is limited to reactive nitriles such as β-cyanocarbonyl (pK_a ~13 in DMSO) and α-arylnitrile (pK_a 21.9 in DMSO) compounds.[3,4] Simple alkylnitriles are among the least acidic carbon pro-nucleophiles (pK_a 31.3 in DMSO, 28.9 in H_2O)[5] and preparation of α-cyano carbanions from alkylnitriles usually requires more than stoichiometric amounts of a strong base in a separate process.[3] Recently, a few methods for catalytic generation of α-cyano carbanions from alkylnitriles were reported;[6] however, the conditions were still highly basic, severely limiting the substrate scope of the electrophile due to the chemoselectivity issue. The catalytic aldol-type addition of α-cyano carbanions generated from non-activated alkylnitriles has been mostly limited to non-enolizable aldehydes,[6] because enolizable, α,α-nonsubstituted aldehydes (pK_a 15.7–16.9 in H_2O)[7] tend to undergo considerable self-condensation under basic conditions. Therefore, it is a formidable task to compensate for the large pK_a gap between alkylnitriles and α,α-nonsubstituted aldehydes to chemoselectively promote the reaction through catalyst control. Herein we report chemoselective *in situ* nucleophilic activation of acetonitrile in the presence of more acidic α,α-nonsubstituted aldehydes using a diphosphine Ru complex and DBU to afford β-hydroxynitriles in good yield (63–90%) (Scheme 1).



Scheme 1

Recently, we reported catalytic generation of α-cyano carbanion of acetonitrile and subsequent addition to non-enolizable aldehydes with a soft Lewis acid–amine base combination.[8] In this system, $CpRu(PPh_3)(CH_3CN)_2PF_6$ (**1a**)[9] (Fig. 1) chemoselectively activates nitrile functionality to lower the pK_a of acetonitrile to be deprotonated by DBU.[10] Considering that DBU itself promoted neither self-condensation of heptanal (**2a**) nor the desired reaction (Table 1, entry 1), we anticipated that chemoselective deprotonation of acetonitrile over more acidic enolizable aldehyde would be possible by combination with an Ru catalyst. With 10 mol% of **1a** and 50 mol% of DBU, chemoselective activation of the acetonitrile occurred at 50 °C to give **3a** with little formation of a self-condensation product, although the chemical yield was unsatisfactory (Table 1, entry 2, 54%) likely due to decomposition of the catalyst caused by the formation of an unstable Ru-DBU complex **6a** in the catalytic cycle (Fig. 2).[11] In the previous report for non-enolizable aldehyde,[8] 10 mol% of $NaPF_6$ was added to prevent the formation of the unfavorable Ru-DBU complex **6a** through cation exchange from *in situ*-formed Ru-alkoxide **5a** into Na-alkoxide and **1a**, enhancing the catalytic efficiency. With enolizable aldehyde **2a**, however, self-condensation of **2a** proceeded extensively in the presence of 10 mol% of $NaPF_6$ and the desired β-hydroxynitrile **3a** was obtained in only 38% yield (Table 1, entry 3). We ascribed the inferior effect of the Na salt to the strong Brønsted basicity of the Na-alkoxide generated *in situ*. Thus, an alternative strategy to accelerate the catalyst regeneration step (**6** to **1** in Fig. 2) without $NaPF_6$ was required to minimize the concentration of the unstable Ru-DBU complex **6**. To address this issue, we chose a Ru-diphosphine complex **1b** (Fig. 1) as a catalyst. ESI-MS analysis of **1a** and **1b** with DBU indicated that **1b** was

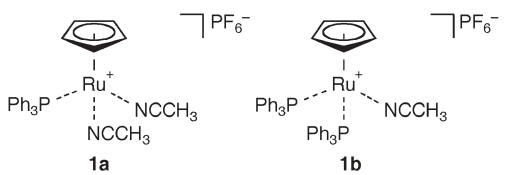
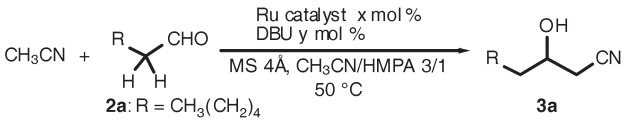


Fig. 1 Structure of Ru complexes **1a** and **1b**.

† Electronic supplementary information (ESI) available: Spectroscopic data of **3** and ESI-MS data of Ru complex-DBU mixture. See http://www.rsc.org/suppdata/cc/b5/b504519c/

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan. E-mail: mshibasa@mol.f.u-tokyo.ac.jp; Fax: +81-3-5684-5206; Tel: +81-3-5841-4830
*mshibasa@mol.f.u-tokyo.ac.jp

Table 1 Optimization of direct addition of acetonitrile to heptanal (**2a**) with cationic Ru complex and DBU[a]



Entry	Ru catalyst	x =	y =	$NaPF_6$ (mol%)	Time (h)	Yield (%)
1	none	0	50	0	24	0
2	$CpRu(PPh_3)(CH_3CN)_2PF_6$ (**1a**)	10	50	0	24	54
3	$CpRu(PPh_3)(CH_3CN)_2PF_6$ (**1a**)	10	50	10	24	38
4	$CpRu(PPh_3)_2(CH_3CN)PF_6$ (**1b**)	10	50	0	10	64
5[b]	$CpRu(PPh_3)_2(CH_3CN)PF_6$ (**1b**)	10	50	0	10	82
6[b]	$CpRu(PPh_3)_2(CH_3CN)PF_6$ (**1b**)	10	25	0	10	76

[a] 0.3 mmol scale. [b] **2a** was added slowly over 7 h.

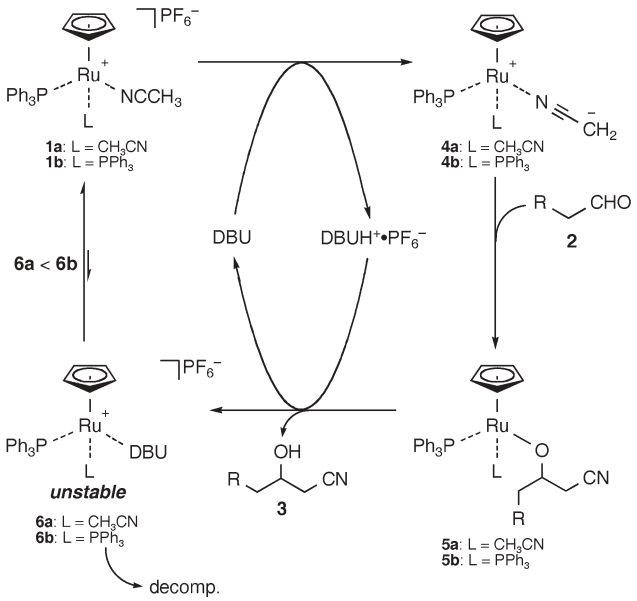
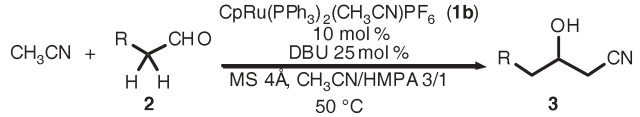


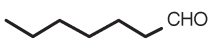
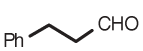
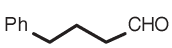
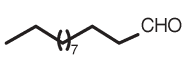
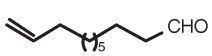
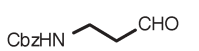
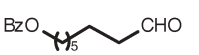
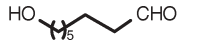
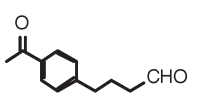
Fig. 2 Proposed catalytic cycle.

much less likely to form the Ru-DBU complex **6b** than the monophosphine complex **1a**, owing to the large steric constraint around the Ru center.[12,13] Thus, the equilibrium between **1b** and **6b** in the catalytic cycle would strongly favor **1b**, accelerating the catalyst regeneration step (**6b** to **1b**). With 10 mol% of **1b** in the absence of $NaPF_6$, the reaction time was reduced to 10 h and the chemical yield was improved to 64% (Table 1, entry 4). The slow addition of **2a** further improved the yield of **3a** to 82% (Table 1, entry 5).[14] The amount of DBU was successfully reduced to 25 mol% and **3a**‡was obtained in 76% yield (Table 1, entry 6).

Having determined the suitable reaction conditions for chemoselective deprotonation of acetonitrile, the reaction was performed with a series of α,α-nonsubstituted aldehydes **2** (Table 2).[15,16] In entries 1–5, deprotonation of acetonitrile proceeded chemoselectively and the subsequent addition to acyclic enolizable aldehydes **2a–d** afforded the desired product in good yield. The reaction with **2e** resulted in moderate yield, probably due to an undesired reaction at the unsaturated bond (entry 6). Carbamate and ester functionality were tolerated without any side reactions (entries 8 and 9). The reaction proceeded smoothly with aldehyde **2i** bearing

Table 2 Addition of acetonitrile to various enolizable aldehydes **2** with diphosphine Ru complex **1b** and DBU[a,b]



Entry	RCH_2CHO		Time (h)	Yield (%)
1		**2a**	10	76
2[c]		**2a**	10	82
3[c]		**2b**	10	77
4		**2c**	10	86
5[d]		**2d**	16	85
6		**2e**	24	63
7		**2f**	14	90
8		**2g**	10	74
9		**2h**	14	82
10[e]		**2i**	12	87
11		**2j**	10	75

[a] 0.3 mmol scale. [b] Aldehyde was added slowly over 7 h. [c] 50 mol% of DBU was used. [d] Aldehyde was added slowly over 12 h. [e] Aldehyde was added as HMPA solution.

a free OH group (87%, entry 10), which is not compatible with reaction conditions using metalated nitriles. **2j** was successfully converted into the corresponding β-hydroxynitrile in 75% yield and the methylketone moiety of **2j** served as neither an electrophile nor a pro-nucleophile under the standard conditions, highlighting the highly chemoselective nature of the present catalysis. When **2c** or **2j** was treated with 10 mol% of KO^{t}Bu at 0 °C, the reaction mixture became complicated and β-hydroxynitrile **3** was obtained in less than 5% yield.

In summary, we developed suitable reaction conditions for chemoselective nucleophilic activation of acetonitrile in the presence of enolizable aldehydes. The use of a stable diphosphine Ru complex gave β-hydroxynitrile **3** in good yield (63–90%). The chemoselective deprotonation despite the large pK_a gap is noteworthy. Further studies to develop an enantioselective variant are in progress.

We thank financial support by Grant-in-Aid for Encouragements for Young Scientists (B) and for Specially Promoted Research from JSPS and MEXT. NK thanks JSPS Research Fellowship for Young Scientists. We thank Dr. M. Kanai and Mr. Y. Suto for useful discussion.

Notes and references

‡ *Representative procedure*: A test tube was charged with magnetic stirrer bar and MS 4A (240 mg) under Ar. MS 4A was flame-dried under reduced pressure (*ca.* 0.7 kPa) for 5 minutes. After cooling, to the flask were added CpRu(PPh$_3$)$_2$(CH$_3$CN)PF$_6$ (**1b**) (500 μL, 0.03 mmol, 0.06 M/CH$_3$CN), dry CH$_3$CN (100 μL) and HMPA (200 μL) successively under Ar and stirred at room temperature. To the mixture was added DBU (11.2 μL, 0.075 mmol) at room temperature, and resulting mixture was degassed. After warming up to 50 °C, heptanal (**2a**) (42.3 μL, 0.3 mmol) was added over 7 h *via* syringe drive. After stirring for 24 h at 50 °C, the mixture was quenched with 1 M HCl and extracted with diethyl ether. The combined organic layers were washed with sat. NaHCO$_3$ aq. and brine, then dried over Na$_2$SO$_4$. The organic solvent was evaporated and resulting crude mixture was purified by flash column chromatography (SiO$_2$, eluent: hexane/ethyl acetate 4/1) to give **3a** (35.3 mg, 0.227 mmol, 76% yield) as a colorless oil.

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8 N. Kumagai, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 13632. In ref. 8, α-mono substituted aldehdye (cyclohexanecarboxaldehyde) was also used as an electrophile. α-Mono substituted aldehdyes are, however, much more robust against self-aldol reaction than α,α-nonsubstituted, linear, aldehdyes due to steric factors.

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10 NMR chemical shift (CDCl$_3$) of Ru(**1a**)-bounded ***CH***$_3$CN was downfielded (^{1}H: δ 2.12 ppm, ^{13}C: δ 3.8 ppm) in comparison with that of free ***CH***$_3$CN (^{1}H: δ 1.93 ppm. ^{13}C: δ 1.97 ppm); For an example of Lewis acid–amine (more than stoichiometric amount) cooperative deprotonation of acetonitrile: T. Sugasawa and T. Toyoda, *Synth. Commun.*, 1979, **9**, 553.

11 Ru-DBU complex was unstable and gradually decomposed to give PPh$_3$=O and Ru black. Furthermore, considering the spatial arrangement of ligands in CpRu-DBU complex, ligated DBU is positioned too far away to deprotonate acetonitrile intramolecularly.

12 See Electronic Supplementary Information (ESI) for details.

13 In the present studies, only CpRu complexes were examined, because bulkier Cp*Ru complexes showed lower reactivity than CpRu complexes in the initial screening using benzaldehyde as an electrophile.

14 Slow addition of **2a** in the presence of NaPF$_6$ resulted in a worse result.

15 Further condensation of product **3** with aldehyde was negligible. Only trace, if any, dehydrated adducts were observed. Sterically less crowded acetonitrile would coordinate more easily to the Ru center than product **3**. In addition, the excess amount of acetonitrile exists in the reaction mixture. Thus, nucleophilic activation of product **3** would effectively be prevented.

16 At the moment, 10 mol% of the Ru complex and 25–50 mol% of DBU are required to obtain products in good yield. Substrate generality of nitriles also remained unsolved. Only acetonitrile was used in the present studies. Further trials to reduce catalyst loading and broaden substrate generality are in progress.

