Carbon–carbon bond forming reactions of *N*-bound transition metal α-cyanocarbanions: a mechanistic probe for catalytic Michael reactions of nitriles†‡

Takeshi Naota,* Akio Tannna and Shun-Ichi Murahashi*

*Department of Chemistry, Graduate School of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka 560-8531, Japan. E-mail: naota@chem.es.osaka-u.ac.jp*

N-Bound α-cyanocarbanion complexes $Ru^+Cp(NCCH^-R^1)(PPh_3)_2$ **1** react with electron deficient olefins to afford the conjugate adduct $Ru^+Cp(NCC^-R^1CHR^2CR^3R^4)(PPh_3)_2$ **2**, kinetic studies of which revealed that complex **1**-catalyzed Michael reactions of nitriles proceed *via* transformation of **1** to **2** and subsequent ligand exchange with nitriles.

Transition metal α-cyanocarbanions have attracted much attention as active species for stoichiometric[1] and catalytic[2,3] carbon–carbon bond formations of nitriles, and studies on their structure and reactivity[4,5] are particularly of importance to develop novel transformations of nitriles bearing high selectivities, atom efficiency and sustainability.[6] In 1989 we presented a new methodology for catalytic carbon–carbon bond formation of nitriles initiated by α-C–H activation of nitriles with low-valent transition metal catalysts.[2a] Capture of the α-cyanocarbanion intermediate with electrophiles provides a family of catalytic C–C bond formations at the α-position of nitriles under neutral conditions.[2] *N*-Bound α-cyanocarbanion complexes, *mer*-$Ru^+H(NCCH^-CO_2R)(NCCH_2CO_2R)(PPh_3)_3$, derived by α-C–H activation of alkyl cyanoacetates with $RuH_2(PPh_3)_4$, have proven to be reactive species and active catalysts for the $RuH_2(PPh_3)_4$-catalyzed aldol and Michael reactions of nitriles.[2b,7] Further studies revealed that a variety of *N*-bound transition metal α-cyanocarbanion complexes act as efficient catalysts for the aldol and Michael reactions of nitriles.[8]

One of the most important aspects of this chemistry is to clarify and control the C–C bond forming process on the α-cyanocarbanion intermediates. Direct nucleophilic attack of zwitterionic *N*-bound α-cyanocarbanions to carbon electrophiles has been postulated for the crucial step in these catalytic aldol and Michael reactions.[2b,3b,7,8] Isomerization to *C*-bound α-cyanocarbanions[5] and subsequent carbometallation[1] are alternative possibilities for this process; however, precise mechanistic information on this step still remains to be explored. During the course of our systematic studies on the structure and reactivity of transition metal α-cyanocarbanions[5] we have succeeded in the isolation of intermediate for catalytic Michael reactions of nitriles. We describe here the conjugate addition of *N*-bound α-cyanocarbanions, $Ru^+Cp(NCCH^-R)(PPh_3)_2$ **1** to electron deficient olefins, and mechanism of the catalytic Michael reactions of nitriles.[9]

When a 25.0 mM solution of *N*-bound α-cyanocarbanion $Ru^+Cp(NCCH^-SO_2Ph)(PPh_3)_2$[5] **1a** in benzene was allowed to react with dimethyl ethylidenemalonate (1.0 equiv.) at room temperature under argon atmosphere, conjugate addition and subsequent 1,3-hydrogen shift occurred to give the corresponding *N*-bound α-cyanocarbanion $Ru^+Cp[NCC^-(SO_2Ph)CH-MeCH(CO_2Me)_2](PPh_3)_2$ **2a** in 99% isolated yield. Complex **2a** was characterized by ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ NMR, IR, mass

spectra and elemental analysis.§ Characteristic downfield shifts of the IR absorption (2153 cm^{-1}) and ^{13}C NMR signal (δ 143.7) of the cyano group indicate that the α-cyanocarbanion is *N*-bound,¶ and the zwitterionic structure has been unequivocally established by a ^1H–^{13}C HMBC experiment.‖ Similar treatment of cyanoacetate and ketonitrile analogs **1b** ($R^1 = CO_2Et$)[8d] and **1c** ($R^1 = COBu^t$) gave the corresponding adducts **2b, c** in 98 and 98% isolated yields. Various electron deficient olefins such as dimethyl benzylidenemalonate, benzylidenemalononitrile, pent-3-en-2-one, and acrylonitrile reacted smoothly with **1a** at room temperature to afford **2d–g** in 98, 99, 31 and 36% yields, respectively.
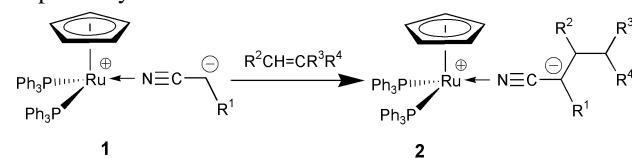
a: $R^1 = SO_2Ph$, $R^2 = Me$, $R^3 = R^4 = CO_2Me$
b: $R^1 = CO_2Et$, $R^2 = Me$, $R^3 = R^4 = CO_2Me$
c: $R^1 = COBu^t$, $R^2 = Me$, $R^3 = R^4 = CO_2Me$
d: $R^1 = SO_2Ph$, $R^2 = Ph$, $R^3 = R^4 = CO_2Me$
e: $R^1 = SO_2Ph$, $R^2 = Ph$, $R^3 = R^4 = CN$
f: $R^1 = SO_2Ph$, $R^2 = Me$, $R^3 = COMe$, $R^4 = H$
g: $R^1 = SO_2Ph$, $R^2 = H$, $R^3 = CN$, $R^4 = H$

As well as complex **1**,[8d] complex **2** shows comparable catalytic activity for the Michael additions of nitriles. Typically, the reaction of (phenylsulfonyl)acetonitrile **4** (4.00 M) with dimethyl benzylidenemalonate **3** (4.40 M) in the presence of **1a** or **2d** catalyst (0.120 M) in THF at 25 °C for 24 h gave adduct **5** in 86 and 88% isolated yields, respectively. In order to obtain insight into the mechanism of the complex **1**-catalyzed Michael addition of nitriles, kinetic studies on the reaction of **1a** with an excess amount of **3** in THF-d_8 were carried out by means of ^1H NMR (500 MHz) analysis using an internal standard (bibenzyl). The consumption rate of **1a** exhibited clean pseudo-first-order dependence on the concentration of **1a** ($k_{obs} = 6.61 \pm 0.04 \times 10^{-4}$ s^{-1} at 25.0 °C, $[\mathbf{1a}]_0 = 2.00 \times 10^{-2}$ M, $[\mathbf{3}]_0 = 2.00 \times 10^{-1}$ M), and the k_{obs} values showed linear dependence on the initial concentration of **3** ranging from 2.00 to 4.00 × 10^{-1} M, indicating the second-order rate constant k_1 as $2.9 \pm 0.1 \times 10^{-3}$ dm^3 mol^{-1} s^{-1} at 25.0 °C. Dependences of k_{obs} *vs.* $[\mathbf{3}]_0$ at 25.0–45.0 °C are shown in Fig. 1. The rate data correlate well ($R^2 = 0.990$) with the Arrhenius relationship of $\ln(k_1)$ *vs.* $1/T$, where the $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values were determined as 41 ± 3 kJ mol^{-1} and -148 ± 8 J mol^{-1} K^{-1}, respectively. The second-order kinetics and the large negative value of $\Delta S^\ddagger$ clearly indicate that the conjugate addition of **1a** to **3** proceeds *via* a direct ionic pathway without any contact of olefins with the metal center. $Ru^+Cp[NCCH(SO_2Ph)CHMeC^-(CO_2Me)_2](PPh_3)_2$ could not be detected during ^1H NMR experiments, indicating that the process involves a fast 1,3-hydrogen shift after the conjugate addition. When complex **2d** was allowed to react with nitrile **4** at room temperature in THF-d_8,
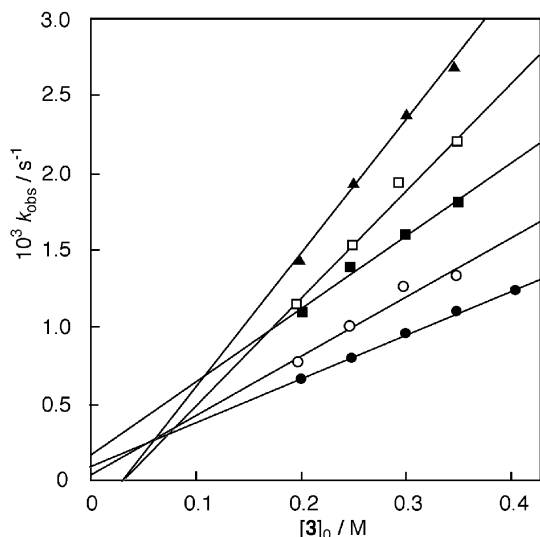
Fig. 1 Dependence of k_{obs} vs. $[3]_0$ for the reactions of **1a** with **3** in THF-d_8 at 25.0 °C (●), 30.0 °C (○) 35.0 °C (■), 40.0 °C (□) and 45.0 °C (▲).

dissociation of Michael adduct **5** and regeneration of complex **1a** can be monitored by ^{1}H NMR spectroscopy. The consumption rate of **2d** was first-order on the concentration of **2d** ($[2d]_0 = 2.00 \times 10^{-2}$ M, $[4]_0 = 2.00 \times 10^{-1}$ M) and independent on the concentration of **4** ($[4]_0 = 2.00–3.50 \times 10^{-1}$ M). The first-order rate constant k_2 was determined to be $7.3 \pm 0.3 \times 10^{-6}$ s^{-1} at 25.0 °C. The observed first-order kinetics on the ligand exchange process is ascribed to rate-determining formation of the 16-electron complex [RuCp(PPh$_3$)$_2$]$^+$ which would be followed by fast rebound process of the carbanion of **4** from outer sphere of the metal.

The complex **1a**-catalyzed Michael reaction of nitrile **4** with olefin **3** can be rationalized by the mechanism shown in Scheme 1. Direct ionic addition of **1a** to **3** and a subsequent 1,3-hydrogen shift affords complex **2d**, which undergoes a rate determining process of ligand exchange with **4** to form adduct **5** and regenerate catalyst **1a**. In order to verify this mechanism, kinetics on the overall catalytic Michael reaction of **4** with **3** were carried out at 25.0 °C in THF-d_8 using the same NMR technique. The initial rate of the formation of **5** was constant (d[**5**]/dt = k_{obs} = $1.44 \pm 0.03 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}), when the reaction was started at an initial concentration of $[1a]_0 = 2.00 \times 10^{-2}$ M, $[3]_0 = 2.00 \times 10^{-1}$ M and $[4]_0 = 2.00 \times 10^{-1}$ M. Almost the same k_{obs} value of $1.49 \pm 0.03 \times 10^{-7}$ dm^3 mol^{-1} s^{-1} was obtained when complex **2d** was employed as the catalyst ($[2d]_0 = 2.00 \times 10^{-2}$ M). These rate constants are first-order on the concentration of catalyst **1a** or **2d**, and zero-order on the concentration of both nitrile **4** and olefin **3**. Thus, the rate law for the catalytic reaction can be expressed as d[**5**]/dt = k_3[Ru] ([Ru] = $[1a]_0 = [2d]_0 = [1a] + [2d]$), which leads to the relation $k_3 = k_{obs}/$[Ru]. The calculated k_3 value of $7.7 \pm 0.9 \times 10^{-6}$ s^{-1} (25.0 °C) is well in accord with that of k_2; the rate constant of rate-determining step of the proposed catalytic cycle.
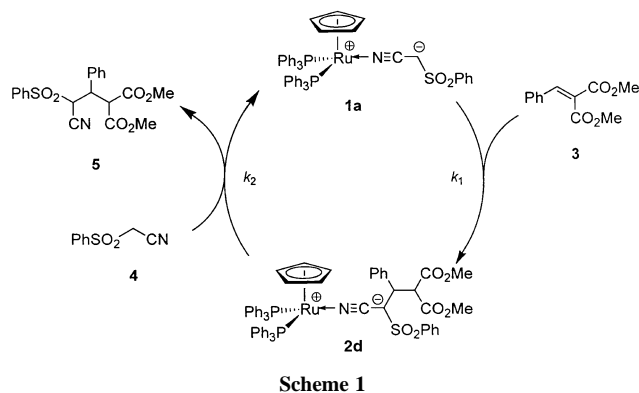
Scheme 1

In summary, we have identified the active species of the catalytic Michael reactions of nitriles, and presented a definitive mechanism for the reactions. This is a rare case because most reported mechanistic investigations for catalytic Michael reactions of nitriles deal mainly with substrate and product analysis while speculating on the crucial step of carbon–carbon bond formation. Efforts are currently underway to investigate more fully the dynamic behavior of transition metal α-cyanocarbanion intermediates in a variety of carbon–carbon bond forming processes of nitriles.

Notes and references

§ *Characterization data* for **2a**: mp 110 °C (decomp.). IR (KBr) 2153 (CN), 1732 (C=O), 1480, 1433, 1281 (C–O, S=O), 1134 (S=O), 1090, 745, 696, 610 cm^{-1}; ^{1}H NMR (500 MHz, C$_6$D$_6$) δ 1.26 (d, J 7.0 Hz, 3 H, CHCH_3), 3.27 (s, 3 H, OCH$_3$), 3.37 (s, OCH$_3$), 3.63 (dq, J 9.6, 7.0 Hz, 1 H, CH^3CH$_3$), 4.11 [d, J 9.6 Hz, 1 H, CH^4(CO$_2$CH$_3$)$_2$], 4.44 (s, 5 H, C$_5$H$_5$), 6.92–7.02 (m, 21 H, ArH), 7.36–7.44 [m, 12 H, PC$_6$H$_5$ (*ortho*)], 8.07 [dd, J 8.0, 2.5 Hz, 2 H, SO$_2$C$_6$H$_5$ (*ortho*)]; ^{13}C{^{1}H} NMR (126 MHz, C$_6$D$_6$) δ 169.5 (C=O), 169.4 (C=O), 150.9 [SO$_2$C$_6$H$_5$ (*ipso*)], 143.7 (CN), 137.9 [PC$_6$H$_5$ (*ipso*)], 134.0 [SO$_2$C$_6$H$_5$ (*ortho*)], 133.8 [PC$_6$H$_5$ (*ortho*)], 129.3 [SO$_2$C$_6$H$_5$ (*para*)], 129.2 [PC$_6$H$_5$ (*para*)], 128.5 [PC$_6$H$_5$ (*meta*)], 126.4 [SO$_2$C$_6$H$_5$ (*meta*)], 83.6 (C$_5$H$_5$), 59.9 [CH(CO$_2$CH$_3$)$_2$], 58.7 (CCN), 52.0 (OCH$_3$), 51.6 (OCH$_3$), 34.2 (CHCH$_3$), 20.4 (CH$_3$); ^{31}P{^{1}H} NMR (202 MHz, C$_6$D$_6$) δ 43.2 (s); FAB-MS: *m/z* 1030 ([M]$^+$). Anal. Calc. for C$_{56}$H$_{51}$NO$_6$P$_2$RuS: C, 65.4; H, 5.00; N, 1.36. Found: C, 65.5; H, 4.82; N, 1.36%.
¶ A variety of *N*-bound complexes RuCp$^+$(NCCH–SO$_2$Ph)(PR$_3$)$_2$ show IR absorption for the CN triple bond in the range *ca.* 2150–2170 cm^{-1}, and ^{13}C chemical shift of a nitrile carbon at δ 140–155, while those of the C-bound isomers have been observed at 2190–2200 cm^{-1} and δ 110–125, respectively.[5]
‖ The ^{1}H NMR signal of **2a** appearing at δ 4.11 strongly correlates with ^{13}C signals of two carbonyl carbons (δ 169.4 and 169.5), which clearly leads to assignment of the ^{1}H signal as the H^4 proton of the zwitterionic α-cyanocarbanion moiety.

1 P. Knochel, N. Jeong, M. J. Rozema and M. C. P. Yeh, *J. Am. Chem. Soc.*, 1989, **111**, 6474; H.-J. Liu and N. H. Al-said, *Tetrahedron Lett.*, 1991, **32**, 5473; T. Kauffmann, H. Kieper and H. Pieper, *Chem. Ber.*, 1992, **125**, 899; M. T. Reetz, H. Haning and S. Stanchev, *Tetrahedron Lett.*, 1992, **33**, 6963.
2 (*a*) T. Naota, H. Taki, M. Mizuno and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1989, **111**, 5954; (*b*) S.-I. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano and A. Fukuoka, *J. Am. Chem. Soc.*, 1995, **117**, 12 436; (*c*) H. Takaya, T. Naota and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1998, **120**, 4244.
3 (*a*) S. Paganelli, A. Schionato and C. Botteghi, *Tetrahedron Lett.*, 1991, **32**, 2807; (*b*) M. Sawamura, H. Hamashima and Y. Ito, *J. Am. Chem. Soc.*, 1992, **114**, 8295; (*c*) Y. Yamamoto, M. Al-Masum and N. Asao, *J. Am. Chem. Soc.*, 1994, **116**, 6019; (*d*) B. M. Trost, P.-Y. Michellys and V. J. Gerusz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1750.
4 S. D. Ittel, C. A. Tolman, A. D. English and J. P. Jesson, *J. Am. Chem. Soc.*, 1978, **100**, 7577; J. G. Stack, J. J. Doney, R. G. Bergman and C. H. Heathcock, *Organometallics*, 1990, **9**, 453; G. L. Crocco, K. E. Lee and J. A. Gladysz, *Organometallics*, 1990, **9**, 2819; J. S. Ricci and J. A. Ibers, *J. Am. Chem. Soc.*, 1971, **93**, 2391.
5 T. Naota, A. Tannna and S.-I. Murahashi, *J. Am. Chem. Soc.*, 2000, **122**, 2960, and references therein.
6 S.-I. Murahashi and T. Naota, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1805.
7 Y. Mizuho, N. Kasuga and S. Komiya, *Chem. Lett.*, 1991, 2127.
8 Ru$^+$H(NCCH–CO$_2$R)(dppe)$_2$: (*a*) M. Hirano, A. Takenaka, Y. Mizuho, M. Hiraoka and S. Komiya, *J. Chem. Soc., Dalton Trans.*, 1999, 3209; Re$^+$(NCCH–CO$_2$R)(NCCH$_2$CO$_2$R)(PMe$_2$Ph)$_4$: (*b*) M. Hirano, Y. Ito, M. Hirai, A. Fukuoka and S. Komiya, *Chem. Lett.*, 1993, 2057; (*c*) M. Hirano, M. Hirai, Y. Ito, T. Tsurumaki, A. Baba, A. Fukuoka and S. Komiya, *J. Organomet. Chem.*, 1998, **569**, 3; RuCp$^+$(NCCH–CO$_2$R)(PPh$_3$)$_2$: (*d*) S.-I. Murahashi, K. Take, T. Naota and H. Takaya, *Synlett*, 2000, 1016.
9 A preliminary result has been presented: *74th Annual Meeting of the Chemical Society of Japan*, Kyotanabe, March 27–30, 1998, Paper 3A117.