Ruthenium catalysis in organic synthesis*

Shun-Ichi Murahashi[1,2,‡], Hikaru Takaya[2], and Takeshi Naota[2]

[1]*Department of Applied Chemistry, Faculty of Engineering, Okayama University of Science, Ridaicho 1-1, Okayama 700-0005, Japan;* [2]*Department of Chemistry, Graduate School of Engineering Science, Osaka University, Machikaneyama 1-3, Toyonaka, Osaka 560-8531, Japan*

Abstract: Ruthenium, rhodium, iridium, and rhenium hydride complexes are highly useful redox Lewis acid and base catalysts. Various substrates bearing hetero atoms are activated by these catalysts and undergo reactions with either nucleophiles or electrophiles under neutral conditions. These types of catalytic reactions are described together with their application to the preparation of various biologically active compounds.

Ruthenium has various valencies (0 to 8 valene) and is not so expensive transition metal; therefore, various useful catalytic reactions for organic synthesis have been explored [1]. It is noteworthy that the medical property of ruthenium is now being recognized, and ruthenium anticancer agents have recently entered the clinic, showing promising activity on resistant tumors. We have developed various ruthenium-catalyzed reactions. Among them, I would like to focus on our findings that low-valent ruthenium hydride complexes can be used as alternatives to the conventional Lewis acids and bases. Furthermore, using iridium, rhodium, and rhenium hydride complexes, various novel and unique catalytic reactions can be explored.

Reactions promoted by Lewis acids and bases are fundamental in organic synthesis; however, most such reactions are merely stoichiometric. Therefore, the development of catalytic reactions that use transition-metal complex catalysts under neutral and mild reaction conditions is particularly important; society needs forward-looking technology, which is based on environmental acceptability. The criteria include atom efficiency, formation of little inorganic waste, and selective synthesis of desired products. We should use instead environmentally friendly catalytic processes that will not produce such waste. If one could design Lewis acid and base catalysts with low redox potentials, their reactions would occur catalytically under neutral conditions. We have, therefore, been searching for transition-metal complex catalysts, which we call redox Lewis acid and base catalysts [2]. We found that divalent ruthenium hydride complexes act as redox Lewis acid catalysts and also as redox base catalysts. Generation of carbon nucleophiles from pronucleophiles by activation of the α-C–H bond adjacent to hetero atoms followed by reaction with various electrophiles affords catalytic carbon–carbon bond forming reactions under neutral and mild reaction conditions. In principle, conventional acids and bases cannot be used at the same time because of neutralization; therefore, we developed Lewis acid base ambiphilic catalysts which can be utilized as either Lewis acid or bases in one-pot reaction. Low-valent ruthenium, iridium, rhodium, and rhenium hydride catalysts can be used as catalysts to replace both Lewis acids and strong bases, and they can be used in combinatorial chemistry.
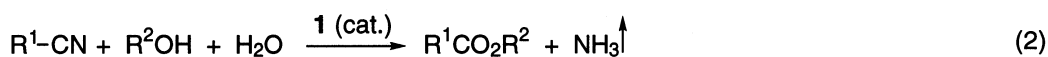

REDOX LEWIS ACID CATALYSTS

Reactions with transition-metal complexes used as redox Lewis acid catalysts will open up new possibilities, because they proceed catalytically with high selectivity under neutral conditions. To explore the possibilities, we focused on low-valent ruthenium dihydride phosphine complexes, because they have low redox potentials, strong coordination ability to heteroatoms, and hydride ligands that are small and labile. The basic concept of redox Lewis acid catalysts has been shown for the activation of nitriles [3]. Nitriles are activated upon coordination to ruthenium complexes. Capture of the ruthenium-coordinated nitriles with various nucleophiles, such as water, alcohols, and amines, provides a new type of catalytic transformation of nitriles that proceeds under neutral conditions. The concept of transition-metal-based Lewis acid catalysts has been shown by Bosnich *et al.* [4]. The underlying principle is used in the design of new kinds of catalytic reactions [5]. However, the above reactions of nitriles with nucleophiles such as amines do not occur with these catalysts. This difficulty may arise if redox processes are important in the reaction.

We found ruthenium hydride complex $RuH_2(PPh_3)_4$ (**1**) catalyzed hydration of nitriles with only 1–2 molar amounts of water under neutral conditions to give the corresponding amides in excellent yields (eq. 1) [6]. The usefulness of the present reaction is illustrated by the synthesis of (–)-pumiliotoxin C, which is an interesting skin alkaloid produced by a Central American frog [7].

$$R-CN + H_2O \xrightarrow{\text{RuH}_2\text{(PPh}_3\text{)}_4 \text{ (1) (cat.)}} R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \tag{1}$$
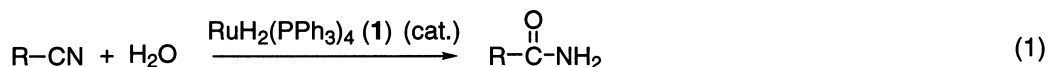
Using the same principle, novel methods for synthesis of esters and amides from nitriles under neutral conditions were discovered. When alcohols are used as nucleophiles, the ruthenium-catalyzed reaction of nitriles with alcohols in the presence of 1–2 molar amounts of water proceeds to give the corresponding esters with evolution of ammonia (eq. 2) [8]. Similar treatment of nitriles with amines gives the corresponding amides along with ammonia (eq. 3) [9].

$$R^1-CN + R^2OH + H_2O \xrightarrow{\text{1 (cat.)}} R^1CO_2R^2 + NH_3\uparrow \tag{2}$$

$$R^1-CN + R^2R^3NH + H_2O \xrightarrow{\text{1 (cat.)}} R^1CONR^2R^3 + NH_3\uparrow \tag{3}$$

The efficiency of these reactions is highlighted by the synthesis of industrially important polyamides as shown in Scheme 1. In the presence of 2 molar amounts of water and catalyst **1**, the reaction of adiponitrile (**2**) with 1,6-hexamethylenediamine (**3**) proceeds to give nylon-6,6 in 98% yield along with ammonia. This process is attractive in comparison with the conventional methods, because (i) the dinitrile **2** can be readily prepared by nickel-catalyzed hydrocyanation of butadiene, (ii) diamine **3** can be readily prepared by nickel-catalyzed hydrogenation of dinitriles, and (iii) polyamides are
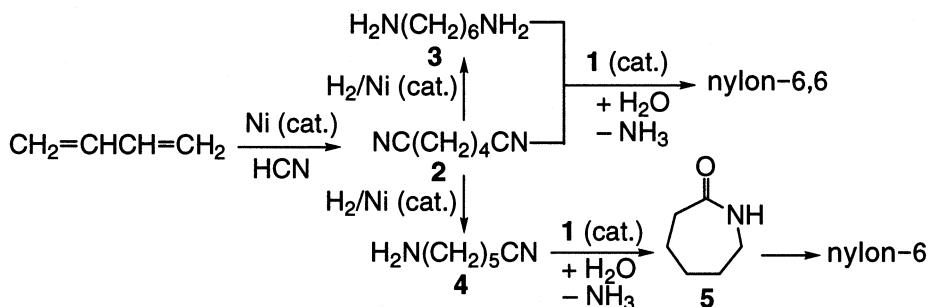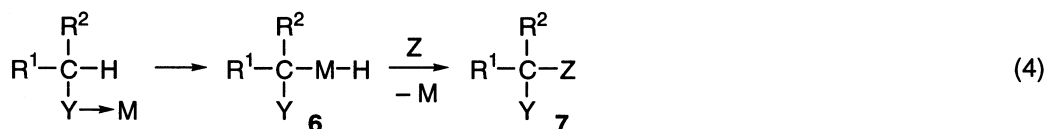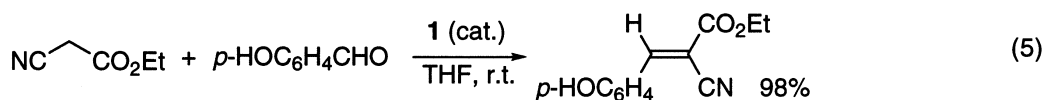
Scheme 1

obtained without formation of salts. Our catalytic process is also useful for synthesis of ε-caprolactam (**5**), which is a precursor of nylon-6. Thus, the ruthenium-catalyzed reaction of aminocapronitrile (**4**), which is derived from catalytic partial hydrogenation of **2** with water, gives **5** selectively.
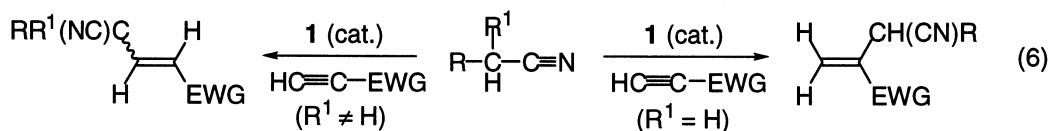
REDOX BASE CATALYSTS

The basic strategy for redox base catalysts has been shown by activations of $C(sp^3)$–H bond α to the heteroatom functions (Y). Coordination of heteroatom to transition metal (M) would increase both the basicity of the metal and the acidity of the α-C–H bond adjacent to Y, and hence oxidative addition of the metal into the α-C–H bond would occur readily to afford α-transition-metalated hydride complex **6**, which can be trapped by insertion of compound (Z) to form a product substituted at the α-position, giving product **7** under neutral conditions (eq. 4). In 1978, we discovered that the activation of

$$R^1-\underset{\underset{Y\rightarrow M}{|}}{\overset{\overset{R^2}{|}}{C}}-H \quad \longrightarrow \quad R^1-\underset{\underset{Y}{|}}{\overset{\overset{R^2}{|}}{C}}-M-H \quad \underset{-M}{\overset{Z}{\longrightarrow}} \quad R^1-\underset{\underset{Y}{|}}{\overset{\overset{R^2}{|}}{C}}-Z \qquad (4)$$

$$\mathbf{6}\mathbf{7}$$

the α-C–H bond of tertiary amines (Y = –NR$_2$) can be performed effectively upon treatment with low-valent transition metals to give imminium ion metal hydride complexes [10]. Since nitriles have stronger coordination ability to metals in comparison with amines, we can expect more readily activation of α-C–H bond. Actually, we found ruthenium-catalyzed carbon–carbon bond forming reactions of nitriles at the α- position of nitriles. In the presence of catalyst **1**, α-C–H activation of nitriles readily proceeds, and Knoevenagel and Michael reactions of nitriles proceed under neutral and mild reaction conditions (eq. 5) [11,12]. This discovery leads to find a family of catalytic carbon–carbon bond-

$$NC\diagdown CO_2Et \ + \ p\text{-}HOC_6H_4CHO \quad \xrightarrow[\text{THF, r.t.}]{\textbf{1 (cat.)}} \quad \underset{p\text{-}HOC_6H_4}{\overset{H}{\diagup}}\underset{CN}{\overset{CO_2Et}{\diagdown}} \quad 98\% \qquad (5)$$

forming reaction of nitriles with electrophiles [13]. The reaction can be rationalized by assuming the mechanism that involves α-C–H activation of nitriles to give C-bonded complex [RCH(CN)RuH] which undergoes isomerization to *N*-bonded complex (RC⁻HCN → Ru⁺H) and subsequent reaction with electrophiles such as carbonyl compounds and alkenes [14]. Actually, we succeeded in isolation of the *C*-bound isomer RuCp[CH(CN)SO$_2$Ph](PR$_3$)$_2$ and the *N*-bound isomer Ru⁺Cp(NCC⁻HSO$_2$Ph)(PR$_3$)$_2$. Interconversion of *C*- and *N*-bound isomers was observed as a key process for the present C–C bond formation [15]. Interestingly, the ruthenium-catalyzed addition of nitriles to terminal acetylenes takes place regioselectively; the addition to the α-position of terminal acetylenes was observed for primary nitriles via *C*-bonded ruthenium complexes, while the addition to the β-position was observed for tertiary nitriles, because of steric requirement of the corresponding ruthenium intermediate (*N*-bonded ruthenium complexes) (eq. 6) [16].

$$\underset{H}{\overset{RR^1(NC)C}{\diagdown}}\underset{EWG}{\overset{H}{\diagup}} \quad \xleftarrow[\substack{HC\equiv C-EWG \\ (R^1 \neq H)}]{\textbf{1 (cat.)}} \quad \underset{H}{\overset{R^1}{\underset{|}{\overset{|}{R-C}}}}-C\equiv N \quad \xrightarrow[\substack{HC\equiv C-EWG \\ (R^1 = H)}]{\textbf{1 (cat.)}} \quad \underset{H}{\overset{H}{\diagup}}\underset{EWG}{\overset{CH(CN)R}{\diagdown}} \qquad (6)$$

The effectiveness of these reactions is demonstrated by the sequential four-component reaction of polymer-supported cyanoacetate **8** (eq. 7) [17]. Thus, the ruthenium-catalyzed four-component reaction of **8** with propionaldehyde, diethyl malonate, and methyl vinyl ketone gave the adduct **9** diastereoselectively (46%, 80% d.e.). It is noteworthy that this type of reaction provides a convenient method for combinatorial chemistry that will be a powerful tool to aid in the rapid discovery of useful molecules.

$$\text{(7)}$$
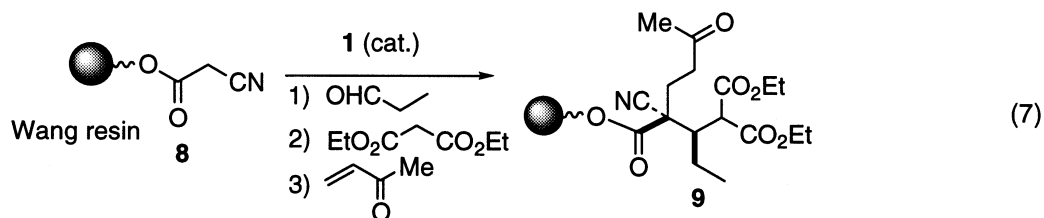
The ruthenium catalysts bearing electron-donating ligands would have higher reactivity to the activation of α-C–H bonds. We found that pentamethylcyclopentadienylrutheniumhydride complex RuCp*H(PPh$_3$)$_2$ (**10**) is a more reactive catalyst, and activation of simple carbonyl compounds can be performed efficiently. Actually, the reaction of cyclopentanone with methyl vinyl ketone in THF at 60 °C in the presence of the catalyst **10** gave **11** in 52% yield (eq. 8). Michael addition of simple ketone is quite difficult, owing to undesirable side reactions; therefore, synthons of ketones, such as enamines and silyl enol ethers, have been used. Therefore, the present direct reaction has an advantage over the conventional methods in view of synthetic and environmental aspects [18].

$$\text{(8)}$$
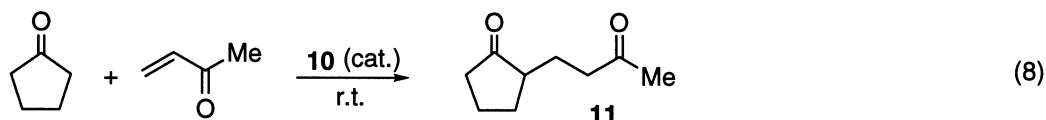
The α-C–H bond activation of isonitriles can be also performed. Coordination of low-valent rhodium complex Rh$_4$(CO)$_{12}$ (**12**) to isonitirls followed by α-C–H bond activation gives α-metalated isonitriles, which undergo reaction with carbonyl compounds. This method can be applied to the synthesis of pyrroles, which are important precursors for biologically active compounds and porphyrins (eq. 9) [19].

$$\text{(9)}$$
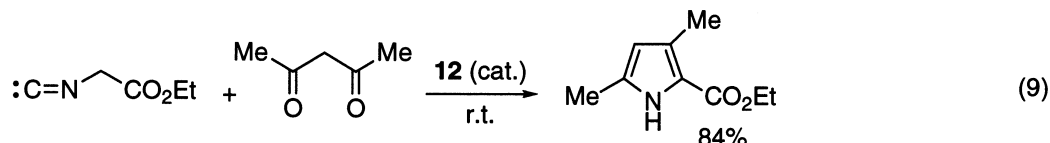
LEWIS ACID-BASE AMBIPHILIC CATALYSTS

Recently, we discovered that iridium hydride complexes IrH(CO)(PPh$_3$)$_3$ (**13**) and IrH$_5$(P-i-Pr$_3$)$_2$ (**14**) can be used as ambiphilic catalysts that work as both Lewis acid and base catalysts. Activation of the α-C–H bonds and the CN triple bonds of nitriles occurs at the same time, and hence cross-addition of nitriles can be performed under neutral conditions to give the corresponding cyanoenamines, which are versatile synthetic intermediates (eq. 10) [20]. This reaction is corresponding to the alternatives to Thorpe–Ziegler reaction which uses strong base such as KH. Typically IrH(CO)(PPh$_3$)$_3$ (**13**)-catalyzed reaction of ethyl cyanoacetate gave cyanoenamine **15** (>99%) from which a building block for antitumor alkaloids **16** was obtained in 96% yield upon treatment with H$_2$SO$_4$ (eq. 11). An important fea-

$$\text{NCCH}_2\text{R}^1 \; + \; \text{NC–R}^2 \xrightarrow{\textbf{13 or 14 (cat.)}} \quad \text{(10)}$$

$$\text{(11)}$$
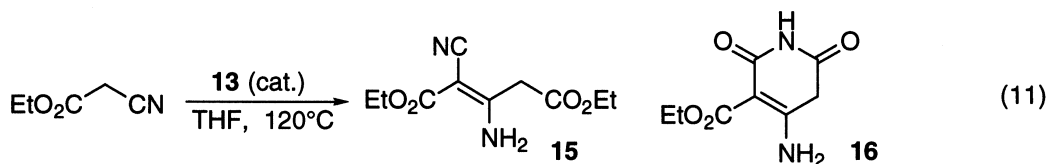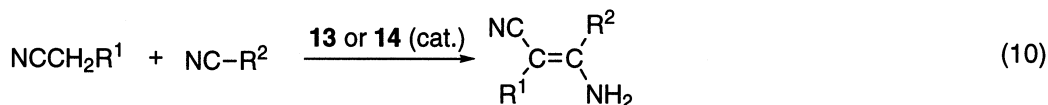
ture of the present reaction is the chemoselective addition of nitriles to the CN triple bonds of nitriles in the presence of carbonyl groups, owing to the strong coordination ability of nitriles toward metals. The iridium-catalyzed addition of ethyl cyanoacetate to 4-acetylbenzonitrile gives ethyl (*Z*)-3-(4-acetylphenyl)-3-amino-2-cyano-2-propenoate chemoselectively, while the same reaction promoted by a conventional base such as $AcONH_4$ gives ethyl 2-cyano-3-(4-cyanophenyl)-2-butenoate.

Recently, we found that rhenium polyhydride complex $ReH_7(PPh_3)_2$ (**17**) is remarkably effective towards the α-C–H activation of carbonyl compounds in the presence of nitriles. Direct α-C–H activation of carbonyl compounds followed by addition to the CN triple bonds of nitriles proceeds efficiently to give the corresponding ketoenamines which are hardly accessible by conventional reactions. Typically, the reaction of **18** and methoxyacetonitrile gave **19** in 84% yield (eq. 12).

$$(12)$$
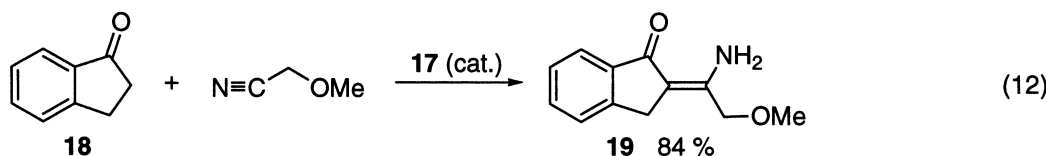
Finally, we developed catalytic multicomponent reactions by using Lewis acid-base ambiphilic catalysts. Multicomponent reactions that involve three or more substrates provide useful strategy not only for combinatorial chemistry but also for minimizing energy, cost, and chemical waste. We found that $IrH_5(P-i-Pr_3)_2$ (**14**) is an effective ambiphilic catalyst, and multicomponent reactions can be performed in one-pot under neutral conditions. Actually, treatment of a mixture of ethyl 2-cyanopropanoate (**20**), acrylonitrile, and water in THF in the presence of catalyst **14** in a sealed tube at 150 °C gave 2-methylglutarimide (**21**, 98%), which is an important building block for biologically active substances (eq. 13). Iridium-catalyzed Michael addition of **20** to acrylonitrile, subsequent multistep hydrations, and cyclocondensation would occur sequentially. At first, the catalyst **14** works as a replacement of base to generate the carbon nucleophile by α-C–H activation. Thereafter, the catalyst **14** works as Lewis acid to promote hydration and cyclocondensation. Using polymer-supported iridium hydride catalyst, this reaction can be applicable to combinatorial chemistry for synthesis of heterocyclic compounds [21].

$$(13)$$
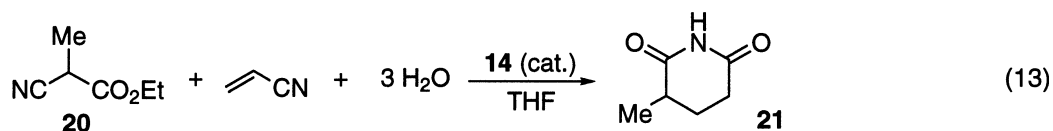
CONCLUSION

The discovery of a new way of chemical reaction often leads to new chemical principles and new application. We discovered that low-valent transition-metal hydride complexes such as ruthenium, iridium, rhodium, and rhenium hydride complexes are highly useful catalysts as redox Lewis acid and base catalysts, and even ambiphilic catalysts. Substrates bearing hetero atoms such as nitriles, isonitriles, and carbonyl compounds can be activated and undergo reactions with either nucleophiles or electrophiles under neutral reaction conditions. The concept will provide a new way that leads to environmentally friendly, future catalytic processes and also to combinatorial chemistry.

REFERENCES

1. T. Naota, H. Takaya, S.-I. Murahashi. *Chem. Rev.* **98**, 2599 (1998)
2. (a) S.-I. Murahashi and H. Takaya. *Acc. Chem. Res.* **33**, 255 (2000); (b) S.-I. Murahashi and T. Naota. *Bull. Chem. Soc. Jpn.* **69**, 1805 (1996).
3. S.-I. Murahashi and T. Naota. *Chemtracts-Org. Chem.* **7**, 281 (1994).

4. B. Bosnich. *Aldrichchimica Acta* **31**, 76 (1998).

5. (a) W. Odenkirk, A. L. Rheingold, B. Bosnich. *J. Am. Chem. Soc.* **114**, 6392 (1992); (b) J. M. Faller and Y. Ma. *Tetrahedron Lett.* **30**, 1189 (1989); (c) E. P. Kündig, C. M. Saudan, G. A. Bernardinelli. *Angew. Chem., Int. Ed.* **38**, 1220 (1999).

6. S.-I. Murahashi, S. Sasao, E. Saito, T. Naota. *J. Org. Chem.* **57**, 2521 (1992).

7. S.-I. Murahashi, S. Sasao, E. Saito, T. Naota. *Tetrahedron* **49**, 8805 (1993).

8. T. Naota, Y. Shichijo, S.-I. Murahashi. *J. Chem. Soc., Chem. Commun.* 1359 (1994).

9. S.-I. Murahashi, T. Naota, E. Saito. *J. Am. Chem. Soc.* **108**, 7846 (1986).

10. (a) S.-I. Murahashi, T. Hirano, T. Yano. *J. Am. Chem. Soc.* **100**, 348 (1978); (b) S.-I. Murahashi and T. Watanabe. *J. Am. Chem. Soc.* **101**, 7429 (1979).

11. T. Naota. H. Taki. M. Mizuno. S.-I. Murahashi. J. *Am. Chem. Soc.* **111**, 5954 (1989).

12. S.-I. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano, A. Fukuoka. *J. Am. Chem. Soc.* **117**, 12436 (1995).

13. (a) S. Paganelli, A. Schionato, C. Botteghi. *Tetrahedron Lett*. **32**, 2807 (1991); (b) M. Sawamura, H. Hamashima, Y. Ito. *J. Am. Chem. Soc.* **114**, 8295 (1992); (c) M. Hirano, Y. Ito, M. Hirai, A. Fukuoka, S. Komiya. *Chem. Lett*. 2057 (1993); (d) Y. Yamamoto, M. Al-Masum, N. Asao. *J. Am. Chem. Soc.* **116**, 6019 (1994); (e) B. M. Trost, P.-Y. Michellys, V. J. Gerusz. *Angew. Chem., Int. Ed. Engl.* **36**, 1750 (1997).

14. T. Naota, A. Tannna, S.-I. Murahashi. *Chem. Commun*. 63 (2001).

15. (a) T. Naota, A. Tannna, S.-I. Murahashi. *J. Am. Chem. Soc.* **122**, 2960 (2000); (b) S.-I. Murahashi, K. Take, T. Naota, H. Takaya. *Synlett* 1016 (2001).

16. S.-I. Murahashi, T. Natota, Y. Nakano, H. Takaya. To be published.

17. H. Takaya and S.-I. Murahashi. *Synlett* 991 (2001).

18. S.-I. Murahashi, X. Zuo, H. Takaya. To be published.

19. H. Takaya, S. Kojima, S.-I. Murahashi. *Org. Lett*. **3**, 421 (2001).

20. H. Takaya, T. Naota, S.-I. Murahashi. *J. Am. Chem. Soc.* **120**, 4244 (1998)

21. H. Takaya and S.-I. Murahashi. To be published.