Homogeneous Catalysis

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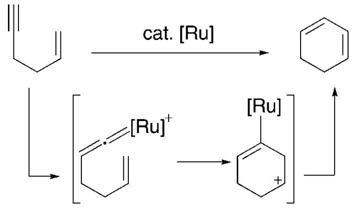
Catalytic Cycloisomerization of 1,5-Enynes to 1,3-Cyclohexadienes via Ruthenium Vinylidene Intermediates**

*Koji Fukamizu, Yoshihiro Miyake, and Yoshiaki Nishibayashi**

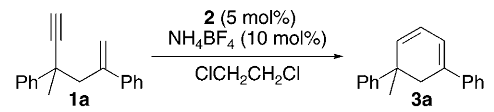
Transition metal-catalyzed cycloisomerization of 1,*n*-enynes is one of the most important strategies for the synthesis of functionalized cyclic structures.[1] This process is attractive as it can increase structural complexity rapidly with relatively simple acyclic subunits and contributes to the concept of atom economy.[2] In particular, 6-*endo*-cycloisomerization of 1,5-enynes is a promising method to afford cyclohexadienes, but successful examples are limited to only a few cases.[1] Recently, Kozmin and his co-workers reported gold- and platinum-catalyzed cycloisomerization of 1,5-enynes to the corresponding cyclohexadienes as a mixture of two isomers, for example, 1,3- and 1,4-cyclohexadienes.[3] In this case, the introduction of a quaternary center at the propargylic position of 1,5-enynes was required for the selective synthesis of 1,3-cyclohexadienes. In several cases, bicyclo[3.1.0]hexenes were formed as the major products.[3,4] Kim and Lee reported rhodium-catalyzed cycloisomerization of *N*-tosyl propargylic enamides to the corresponding 1,2-dihydropyridines via rhodium vinylidene[5] complexes as key intermediates.[6] In this case, only *N*-tosyl propargylic enamides were used as substrates. We have so far reported the ruthenium-catalyzed preparation of 1,5-enynes and some of their transformations.[7] During further investigations on this subject, we developed the ruthenium-catalyzed cycloisomerization of 1,5-enynes to 1,3-cyclohexadienes via ruthenium vinylidene intermediates (Scheme 1).[5] The method described herein may provide a selective synthetic route to 1,3-cyclohexadienes from the corresponding 1,5-enynes incorporating both quaternary and tertiary stereogenic centers at the propargylic position.



Scheme 1. Carbon–carbon bond-forming cycloisomerization of 1,5-enynes via ruthenium vinylidene complexes as key intermediates.

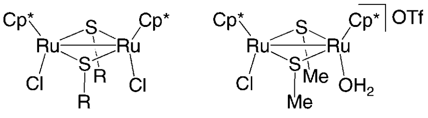
Heating of 2,4-diphenyl-4-methyl-1-hexen-5-yne (**1a**) in $ClCH_2CH_2Cl$ at 80 °C for 48 h in the presence of 5 mol% of the methanethiolate-bridged diruthenium complex[8] $[\{Cp^*RuCl(\mu_2\text{-}SMe)\}_2]$ (**2a**; $Cp^* = \eta^5\text{-}C_5Me_5$) and 10 mol% of NH_4BF_4 gave 1,5-diphenyl-5-methyl-1,3-cyclohexadiene (**3a**) in 97% yield (Table 1, entry 1). This reaction proceeded smoothly even at 40 °C, but a prolonged reaction time was necessary (Table 1, entry 2). Both the complex $[\{Cp^*RuCl(\mu_2\text{-}S\textit{i}Pr)\}_2]$ (**2b**), which bore a sterically more demanding moiety, and the cationic diruthenium complex $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*(OH_2)]OTf$ (**2c**; $OTf = OSO_2CF_3$) exhibited a lower catalytic activity (Table 1, entries 3 and 4). Mononuclear ruthenium and rhodium complexes, such as $[CpRuCl(PPh_3)_2]$ ($Cp = \eta^5\text{-}C_5H_5$),[9] $[(C_9H_7)RuCl(PPh_3)_2]$, $[RuCl_2(\textit{p}\text{-}cymene)PPh_3]$,[10] $[TpRu(PPh_3)(CH_3CN)_2]PF_6$[11] (Tp = tris(1-pyrazolyl)borate), and $[RhCl(PPh_3)_3]$, did not promote this cycloisomerization effectively. Notably, no cycloisomerization took place when $PtCl_2$ was used as a catalyst.[3]

Table 1: Ruthenium-catalyzed cycloisomerization of 2,4-diphenyl-4-methyl-1-hexen-5-yne (**1a**) to 1,5-diphenyl-5-methyl-1,3-cyclohexadiene (**3a**).



Entry	Catalyst	*T* [°C]	*t* [h]	Yield [%][a]
1	$[Cp^*RuCl(\mu_2\text{-}SMe)_2]$ (**2a**)	80	48	97
2	$[Cp^*RuCl(\mu_2\text{-}SMe)_2]$ (**2a**)	40	72	92
3	$[Cp^*RuCl(\mu_2\text{-}S\textit{i}Pr)_2]$ (**2b**)	80	48	37
4	$[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*(OH_2)]OTf$ (**2c**)	80	48	16

[a] Yield of isolated product.



R = Me (**2a**), *i*Pr (**2b**) **2c**

Next, cycloisomerization of a variety of 1,5-enynes was carried out at 40 °C by using **2a** as a catalyst (Table 2). The introduction of a methyl or a phenyl group to the phenyl substituent of the alkene moiety gave the corresponding 1,3-cyclohexadienes (**3b** and **3c**) in 96% and 97% yields, respectively (Table 2, entries 2 and 3). Reactions of 1,5-enynes bearing a chloro- or bromophenyl substituent at the

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[*] K. Fukamizu, Dr. Y. Miyake, Prof. Dr. Y. Nishibayashi
Institute of Engineering Innovation, School of Engineering
The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo, 113-8656 (Japan)
Fax: (+81)3-5841-1175
E-mail: ynishiba@sogo.t.u-tokyo.ac.jp
Homepage: http://park.itc.u-tokyo.ac.jp/nishiba/

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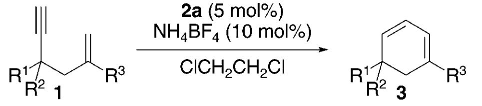
Table 2: Ruthenium-catalyzed formation of 1,3-cyclohexadienes (**3**).[a]



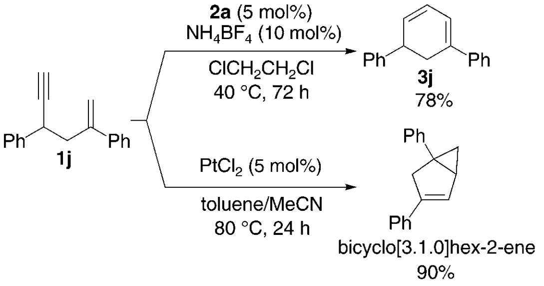
Entry	**1**	T [°C]	t [h]	Yield [%][b]
1	R^1 = Ph, R^2 = Me, R^3 = Ph (**1a**)	40	72	92 (**3a**)
2	R^1 = Ph, R^2 = Me, R^3 = p-MeC$_6$H$_4$ (**1b**)	40	72	96 (**3b**)
3	R^1 = Ph, R^2 = Me, R^3 = p-PhC$_6$H$_4$ (**1c**)	40	72	97 (**3c**)
4	R^1 = Ph, R^2 = Me, R^3 = p-ClC$_6$H$_4$ (**1d**)	40	192	95 (**3d**)
5	R^1 = Ph, R^2 = Me, R^3 = p-BrC$_6$H$_4$ (**1e**)	40	216	95 (**3e**)
6	R^1 = ^{n}Pr, R^2 = Me, R^3 = Ph (**1f**)	40	72	92 (**3f**)
7	R^1 = Et, R^2 = Et, R^3 = Ph (**1g**)	40	120	96 (**3g**)
8	R^1, R^2 = −(CH$_2$)$_2$−, R^3 = Ph (**1h**)	40	96	44 (**3h**)
9	R^1, R^2 = −(CH$_2$)$_5$−, R^3 = Ph (**1i**)	40	120	93 (**3i**)
10	R^1 = Ph, R^2 = H, R^3 = Ph (**1j**)	40	72	78 (**3j**)
11	R^1 = ^{n}Pr, R^2 = H, R^3 = Ph (**1k**)	40	96	82 (**3k**)
12	R^1 = Ph, R^2 = H, R^3 = H (**1l**)	80	24	0 (**3l**)[c]

[a] All reactions of **1** (0.20 mmol) were carried out in the presence of **2a** (0.01 mmol) and NH$_4$BF$_4$ (0.02 mmol) in ClCH$_2$CH$_2$Cl (1 mL). [b] Yield of isolated product. [c] Dimerization of **1l** took place.

alkene moiety were sluggish and a longer reaction time was necessary. However, in both cases, the corresponding cyclohexadienes (**3d** and **3e**) were obtained in excellent yields (Table 2, entries 4 and 5). Excellent yields of 1,3-cyclohexadienes (**3f** and **3g**) were also obtained from reactions of 1,5-enynes bearing two alkyl moieties at the propargylic position (Table 2, entries 6 and 7). The introduction of a cyclopropane moiety at the propargylic position of 1,5-enyne slightly decreased the yield of the corresponding spirocyclic 1,3-cyclohexadiene (**3h**; Table 2, entry 8), whereas the use of a cyclohexane moiety in place of a cyclopropane moiety afforded the corresponding spirocyclic compound (**3i**) in an excellent yield (Table 2, entry 9). Cycloisomerization of 1,5-enynes bearing a tertiary center at the propargylic position under the same reaction conditions afforded the corresponding 1,3-cyclohexadienes (**3j** and **3k**) in high yields (Table 2, entries 10 and 11). The molecular structure of **3j** was confirmed by X-ray analysis.[12] Unfortunately, no cycloisomerization occurred at all when 4-phenyl-1-hexen-5-yne (**1l**) was used as a substrate (Table 2, entry 12).

Kozmin and co-workers reported the PtCl$_2$-catalyzed cycloisomerization of 1,5-enynes into the corresponding isomeric cyclohexadienes.[3] However, when we carried out the reaction of **1j** in the presence of a catalytic amount of PtCl$_2$ according to their procedure,[3] only 3,5-diphenylbicyclo[3.1.0]hex-2-ene was obtained in 90% yield without the formation of **3j** [Eq. (1)], which indicates that Kozmin's system is not applicable to the formation of **3j** from **1j**.

Cycloisomerization of 1,5-enynes incorporating a heterocycle (**4**) also proceeded smoothly to give the corresponding tricyclic 1,3-cyclohexadienes (**5**) in high yields (Scheme 2). When an alkyl substituent, such as tBu, was introduced to the alkene moiety (**4a**), the corresponding cyclic compound (**5a**) was obtained in 88% yield. Separately, we confirmed that optically active 1,5-enyne (**4e**) can be converted into the cyclic compound **5e** without any loss of optical purity.



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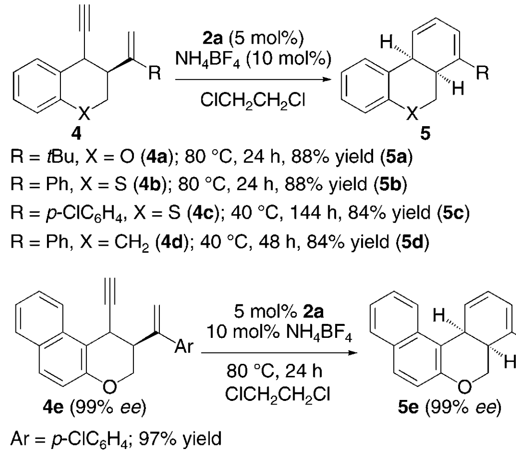


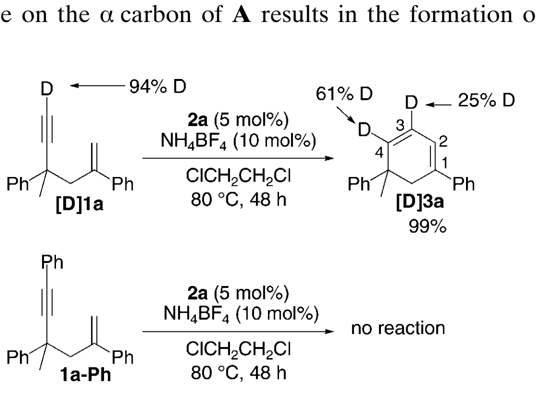
R = tBu, X = O (**4a**); 80 °C, 24 h, 88% yield (**5a**)
R = Ph, X = S (**4b**); 80 °C, 24 h, 88% yield (**5b**)
R = p-ClC$_6$H$_4$, X = S (**4c**); 40 °C, 144 h, 84% yield (**5c**)
R = Ph, X = CH$_2$ (**4d**); 40 °C, 48 h, 84% yield (**5d**)

Ar = p-ClC$_6$H$_4$; 97% yield

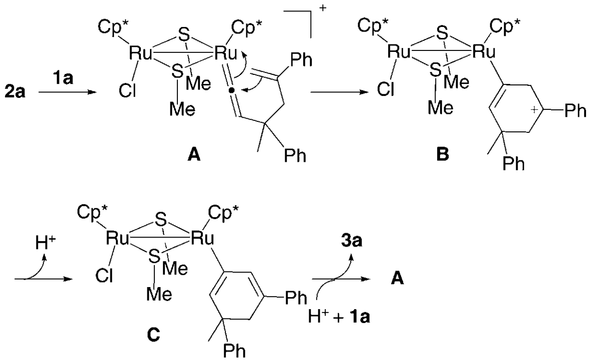
Scheme 2. Ruthenium-catalyzed cycloisomerization of 1,5-enynes incorporating a heterocycle.

To gain an insight into the reaction pathway, we investigated the cyclization of a 1,5-enyne bearing a deuterium atom at the terminal position of the alkyne moiety (**[D]1a**; Scheme 3). The deuterated cyclohexadiene **[D]3a** was isolated in 99% yield with 25% and 61% deuterium incorporation at the 3- and 4-positions, respectively. When we attempted the cycloisomerization of 1,5-enyne **1a-Ph**, bearing an internal alkyne moiety, under the same reaction conditions, no formation of the cyclic compound was detected and 93% of unreacted **1a-Ph** was recovered.

By considering the above experimental results, a reaction pathway is proposed in Scheme 4. Initially, a vinylidene complex **A** is formed from the reaction of **1a** with **2a** in the presence of NH$_4$BF$_4$. Intramolecular nucleophilic attack of an alkene on the α carbon of **A** results in the formation of an



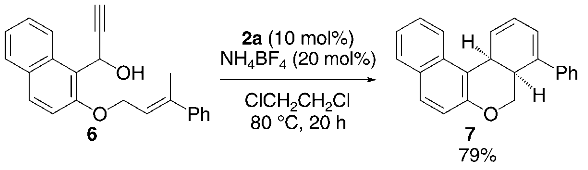
Scheme 3. Ruthenium-catalyzed cycloisomerization of 1,5-enynes.



Scheme 4. Proposed reaction pathway for ruthenium-catalyzed cycloisomerization of 1,5-enynes.

alkenyl complex **B**. Subsequent deprotonation gives the cyclic compound **3a** via another alkenyl complex **C**. Considering the low activity of mononuclear complexes, we believe that the synergistic effect[13] in the diruthenium complexes is also important for promotion of this catalytic reaction. The incomplete deuterium incorporation at the 4-position may be due to H/D exchange.[14]

Finally, this methodology of the selective synthesis of 1,3-cyclohexadienes may be extended to one-pot catalytic sequential reaction in combination with the ruthenium-catalyzed carbon–carbon bond-forming reaction, giving 1,5-enynes via the allenylidene–ene pathway.[7] Treatment of a propargylic alcohol with an (*E*)-alkene moiety (**6**) in the presence of a catalytic amount of **2a** (10 mol%) in $ClCH_2CH_2Cl$ at 80 °C for 20 h gave the 1,3-cyclohexadiene **7** in 79% yield (Scheme 5). The molecular structure of **7** was confirmed by X-ray analysis.[15] This sequential reaction provides a conceptually new type of [3+3]cycloaddition system between propargylic alcohols and alkenes.[16]



Scheme 5. Ruthenium-catalyzed sequential reaction of propargylic alcohol bearing an alkene moiety.

In summary, the ruthenium-catalyzed 6-*endo*-cycloisomerization of 1,5-enynes gave the corresponding 1,3-cyclohexadienes in high to excellent yields. We consider this reaction to proceed via ruthenium vinylidene complexes as key intermediates. Although many examples of coupling reactions between alkynes and alkenes have been reported to date, but this reaction is the first successful example of ruthenium-catalyzed cycloisomerization of 1,5-enynes to 1,3-cyclohexadienes.[1] We believe that this finding will open up a new aspect of metal vinylidene chemistry.[5] The novel synthetic and catalytic method described herein constitutes another way to selectively prepare 1,3-cyclohexadienes. This cyclic diene skeleton is a core subunit in many natural products and a useful building block for a variety of transformations in organic chemistry and materials science.[17,18] Further work is currently in progress to apply this reaction to the total synthesis of natural products.

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[1] For recent reviews of cycloisomerization of 1,*n*-enynes, see: a) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813; b) L. Añorbe, G. Domínguez, J. Pérez-Castells, *Chem. Eur. J.* **2004**, *10*, 4938; c) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431; d) C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328; e) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271; f) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; g) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; h) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; i) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268.

[2] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.

[3] a) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806; b) J. Sun, M. P. Conley, L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2006**, *128*, 9705.

[4] a) J. Blum, H. Beer-Krafts, Y. Badrieh, *J. Org. Chem.* **1995**, *60*, 5567; b) A Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785; c) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654; d) Y. Harrak, C. Blazykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mouriés, A. L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2004**, *126*, 8656.

[5] For recent reviews on catalytic transformation via a metal vinylidene intermediate, see: a) C. Bruneau, P. H. Dixneuf, *Angew. Chem.* **2006**, *118*, 2232; *Angew. Chem. Int. Ed.* **2006**, *45*, 2176; b) J. A. Varela, C. Saá, *Chem. Eur. J.* **2006**, *12*, 6450; c) B. M. Trost, A. MacClory, *Chem. Asian J.* **2008**, *3*, 164; d) *Metal Vinylidenes and Allenylidenes in Catalysis* (Eds.: C. Bruneau, P. H. Dixneuf), Wiley-VCH, Weinheim, **2008**.

[6] H. Kim, C. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 6336.

[7] a) Y. Nishibayashi, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 6060; b) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2004**, *126*, 16066; c) K. Fukamizu, Y. Miyake, Y. Nishibayashi, *J. Am. Chem. Soc.* **2008**, *130*, 10498.

[8] For the preparation and X-ray analysis of a variety of chalcogenolate-bridged diruthenium complexes, as well as their catalytic activity toward the propargylic substitution reactions, see: a) Y. Nishibayashi, H. Imajima, G. Onodera, M. Hidai, S. Uemura, *Organometallics* **2004**, *23*, 26; b) Y. Nishibayashi, H. Imajima, G. Onodera, Y. Inada, M. Hidai, S. Uemura, *Organometallics* **2004**, *23*, 5100.

[9] The intermolecular coupling reactions between alkynes and alkenes catalyzed by $[CpRuCl(PPh_3)_2]$ have been reported, see: a) M. Murakami, M. Ubukata, Y. Ito, *Tetrahedron Lett.* **1998**, *39*, 7361; b) M. Murakami, M. Ubukata, Y. Ito, *Chem. Lett.* **2002**, *31*, 294.

[10] Merlic and Pauly reported the cycloisomerization of dienylalkynes catalyzed by $[RuCl_2(p\text{-cymene})PPh_3]$, see: C. A. Merlic, M. E. Pauly, *J. Am. Chem. Soc.* **1996**, *118*, 11319.

[11] Liu and co-workers reported the cycloisomerization of (*o*-ethynyl)styrenes catalyzed by $[TpRu(PPh_3)(CH_3CN)_2]PF_6$. See: a) H.-C. Shen, S. Pal, J.-J. Lian, R.-S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 15762; b) J.-J. Lian, A. Odedra, C.-J. Wu, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 4186.

[12] The molecular structure of **3j** was confirmed by X-ray analysis. CCDC 713509 (**3j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] a) Y. Nishibayashi, M. D. Milton, Y. Inada, M. Yoshikawa, I. Wakiji, M. Hidai, S. Uemura, *Chem. Eur. J.* **2005**, *11*, 1433; b) S. C. Ammal, N. Yoshikai, Y. Inada, Y. Nishibayashi, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 9428.

[14] A similar H/D exchange has been detected in several cases. See: a) K.-L. Yeh, B. Liu, C.-Y. Lo, R.-S. Liu, *J. Am. Chem. Soc.* **2002**, *124*, 6510; b) A. Odedra, C.-J. Wu, T. B. Pratap, C.-W. Huang, Y.-F. Ran, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 3406; c) H. Kim, C. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 10180.

[15] The molecular structure of **7** was confirmed by X-ray analysis. CCDC 713508 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] For a recent review, see: *Metal-Catalyzed Cascade Reactions* (Ed.: T. J. J. Müller), Springer, Heidelberg, **2006**.

[17] For reviews, see: a) *Classics in Total Synthesis* (Eds.: K. C. Nicolaou, E. J. Sorensen), Wiley-VCH, Weinheim, **1996**; b) *Classics in Total Synthesis II* (Eds.: K. C. Nicolaou, S. A. Snyder), Wiley-VCH, Weinheim, **2003**.

[18] For reviews, see: a) J.-E. Bäckvall, R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **1998**, *98*, 2291; b) M. Irie, *Chem. Rev.* **2000**, *100*, 1685; c) K. Matsuda, M. Irie, *Chem. Lett.* **2006**, *35*, 1204; d) M. Irie, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 917.