DOI: 10.1002/ejoc.200800771

Hydrolytic Deallylation of *N*-Allyl Amides Catalyzed by Pd^{II} Complexes

Naoya Ohmura,[a] Asami Nakamura,[a] Akiyuki Hamasaki,[a] and Makoto Tokunaga*[a]

Keywords: Amides / Allylic compounds / Hydrolysis / Homogeneous catalysis / Palladium

Hydrolytic deallylation of *N*-allyl amides to give amides and propanal can be achieved with Pd^{II} catalysts. The optimized catalyst consists of $Pd(OCOCF_3)_2$ and 1,3-bis(diphenylphosphanyl)propane (DPPP). Several kinds of open-chain *N*-allyl amides and *N*-allyl lactams undergo hydrolytic deallylation to give the corresponding amides and lactams in good to high yield. A mechanism which includes isomerization to enamides and subsequent hydrolysis is proposed.

Introduction

The allyl group is one of the most versatile protecting groups in organic synthesis. This group is used for the protection of various functional groups such as alcohols, phenols, carboxylic acids, phosphoric acids, amines and amides because of its stability towards both acidic and basic conditions.[1] A traditional approach for deprotection of the allyl group is isomerization to the 1-propenyl group and subsequent hydrolysis or oxidation.[1] In recent decades, several single-step mild deprotection procedures have been developed including Pd-catalyzed Tsuji–Trost reaction-based methods,[2] Rh-[2c] and Ru-catalyzed[3] hydrolysis or alcoholysis. However, in spite of the importance of amides and lactams in pharmacology and natural product chemistry, there are only few single-step procedures for the cleavage of the allyl group from nitrogen. In a pioneering work for using the allyl group for the protection of nitrogen in a β-lactam synthesis, it took four steps for the removal.[4] The use of current ruthenium chemistry allows a two-step sequence:[5] isomerization to the 1-propenyl isomer with a Grubbs-type catalyst, then cleavage leading to the N–H form by $NaIO_4$ oxidation with $RuCl_3$ as a catalyst.[5c,5d] More recently, two types of one-pot deallylation methods have been reported.[6,7] Zacuto et al. developed a one-pot deallylation method using unadorned $RhCl_3$ as catalyst and 1-propanol as reagent.[6] The key to success in this case is the dual function of $RhCl_3$ in alcohol solvents, which provides an active rhodium hydride species that catalyzes the isomerization of *N*-allyl amides to the corresponding enamides but also generates HCl to hydrolyze to amides. Cadierno et al. developed a Ru^{IV}-complex-catalyzed method in which the complex also catalyzes both the isomerization step to enamides and the oxidative cleavage step with stoichiometric KIO_4.[7] This method is applicable for a wide range of substrates to provide the products in high yields, however, alkene or diol functional groups may be oxidized at the same time. Since we have focused on utilizing water and alcohols as reagent for organic reactions,[8] we have explored the possibilities of hydrolytic deallylation of *N*-allyl amides. This paper describes the first one-pot deallylation of *N*-allyl amides using Pd^{II} catalysts employing water as reagent which possess high atom efficiency.

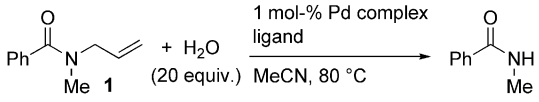
Results and Discussion

The hydrolysis of *N*-allyl amides was examined with several Pd precursors and ligands. *N*-Allyl-*N*-methylbenzamide (**1**) was chosen for the screening, 1 mol-% of catalyst and 20 equiv. of water in MeCN were stirred at 80 °C for 20–24 h (Table 1). When $PdCl_2(MeCN)_2$ was used as palladium source, reactions in the absence of ligand gave almost no conversion of **1** (Table 1, entry 1), and the addition of 5,5′-dimethylbipyridine did not improve the catalytic activity (Table 1, entry 2). However, the hydrolyzed amide was obtained in 41% yield when PPh_3 was added as ligand (Table 1, entry 3). When $Pd(OCOMe_3)_2$ was used, the substrate **1** remained intact under the examined conditions (Table 1, entries 4 and 5). Generally higher conversions were observed when $Pd(OCOCF_3)_2$ was used as catalyst precursor. In the absence of a ligand, the product was obtained in 2% yield (Table 1, entry 6), addition of pyridine derivatives decreased the activity (Table 1, entries 7 and 8). Increased activity was observed in the presence of phosphane ligands (Table 1, entries 9–23). Among the tested monodentate ligands, S-Phos showed the highest activity and the product was obtained in 81% yield (Table 1, entry 12). On the other hand, bidentate phosphanes were also effective for the reaction. In both cases, P/Pd = 2 exhibited the best performance in this reaction. When P/Pd was lower

[a] Department of Chemistry, Graduate School of Science, Kyushu University
6-10-1, Hakozaki, Higashi-ku 812-8581, Japan
Fax: +81-92-642-7528
E-mail: mtok.scc@mbox.nc.kyushu-u.ac.jp
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

than 2, rapid formation of Pd-black was observed, however, when the ratio was larger than 2, the reaction became sluggish. Among the examined bidentate ligands, DPPP was found to be most effective and afforded the hydrolyzed product in 92% yield (Table 1, entry 17). DPPP in combination with a different Pd source, such as $PdCl_2(MeCN)_2$ and $Pd(OCOMe)_2$, was examined but yields were low (Table 1, entries 18 and 19), therefore we conclude that $Pd(OCOCF_3)_2$/DPPP is the optimized catalyst system.

Table 1. Pd-catalyzed hydrolytic deallylation of 1.[a]



Entry	Catalyst	Ligand	Time [h]	Yield [%]
1	$PdCl_2(MeCN)_2$	none	20	1
2	$PdCl_2(MeCN)_2$	5,5′-dimethylbipyridine[b]	20	0
3	$PdCl_2(MeCN)_2$	PPh_3[c]	20	41
4	$Pd(OCOMe)_2$	none	20	0
5	$Pd(OCOMe)_2$	PPh_3[c]	20	0
6	$Pd(OCOCF_3)_2$	none	24	2
7	$Pd(OCOCF_3)_2$	5,5′-dimethylbipyridine[b]	24	3
8	$Pd(OCOCF_3)_2$	pyridine[c]	24	0
9	$Pd(OCOCF_3)_2$	PPh_3[c]	20	67
10	$Pd(OCOCF_3)_2$	$P(4\text{-}CF_3C_6H_4)_3$[c]	20	18
11	$Pd(OCOCF_3)_2$	$P(cyclohexyl)_3$[c]	20	7
12	$Pd(OCOCF_3)_2$	S-Phos[c,d]	20	81
13	$Pd(OCOCF_3)_2$	BINAP[b,e]	20	12
14	$Pd(OCOCF_3)_2$	XANTPHOS[b,f]	20	5
15	$Pd(OCOCF_3)_2$	DPPM[b, g]	20	38
16	$Pd(OCOCF_3)_2$	DPPE[b,h]	20	58
17	$Pd(OCOCF_3)_2$	DPPP[b,i]	20	92
18	$PdCl_2(MeCN)_2$	DPPP[b,i]	20	34
19	$Pd(OCOMe)_2$	DPPP[b,i]	20	1
20	$Pd(OCOCF_3)_2$	DPPB[b,j]	20	83
21	$Pd(OCOCF_3)_2$	DPPPent[b,k]	24	43
22	$Pd(OCOCF_3)_2$	DPPHex[b,l]	24	36
23	$Pd(OCOCF_3)_2$	DPPF[b,m]	20	32

[a] The reactions were carried out on 1-mmol scale and the yield was determined by GC analysis. [b] 1 mol-% of ligand was used. [c] 2 mol-% of ligand was used. [d] S-Phos: 2-dicyclohexylphosphanyl-2′,6′-dimethoxy-1,1′-biphenyl. [e] BINAP: 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl. [f] XANTPHOS: 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene. [g] DPPM: 1,1-Bis(diphenylphosphanyl)methane. [h] DPPE: 1,2-Bis(diphenylphosphanyl)ethane. [i] DPPP: 1,3-Bis(diphenylphosphanyl)propane. [j] DPPB: 1,4-Bis(diphenylphosphanyl)butane. [k] DPPPent: 1,5-Bis(diphenylphosphanyl)pentane. [l] DPPHex: 1,6-Bis(diphenylphosphanyl)hexane. [m] DPPF: 1,1′-Bis(diphenylphosphanyl)ferrocene.

Table 2 displays solvent effects on this reaction. Several water-miscible solvents were tested and acetonitrile was found to be the best solvent (Table 2, entry 5, cf. entries 1–4). In this study, the reactions were generally conducted under N_2 atmosphere, while slight decrease of the product yield was observed when the reactions were carried out under air atmosphere. Then substrate generality was explored with an optimized catalyst system. Several kinds of *N*-allyl amides (**1**–**11**) were examined with 2–5 mol-% Pd-$(OCOCF_3)_2$/DPPP catalyst (Table 3). The reactions with open-chain substrates **1**–**4** proceeded smoothly and afforded the hydrolyzed product almost quantitatively (Table 3, entries 1–4). However, the four-, five- and six-membered cyclic substrates **5**–**7** were found to have lower reactivity. Using higher catalyst loadings (5 mol-%), **7** was hydrolyzed to give the desired product in 99% yield, however, **5** and **6** gave the product only in moderate yield and mainly 1-propenyl amides remained unhydrolyzed (Table 3, entries 5–7). Lactam substrates having a seven- (**8**), or eight-membered ring (**9**) readily underwent the hydrolysis reaction (Table 3, entries 8 and 9). The reactions with the *N*-allylcarbamates **10** and **11** afforded the products in good yield (100 and 90%, Table 3, entries 10

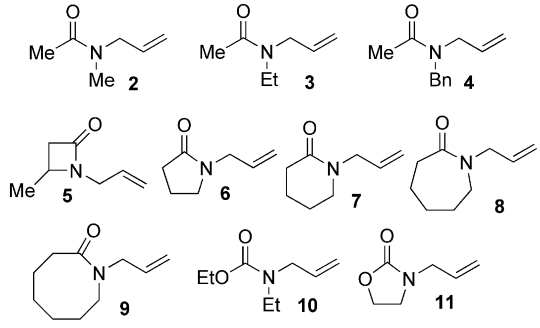
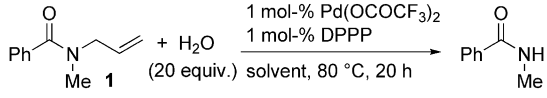


Table 2. Solvent effect on the Pd-catalyzed hydrolytic deallylation of **1**.[a]



Entry	Solvent	Yield [%]
1	THF	18
2	DME	26
3	1,4-dioxane	26
4	2-propanol	50
5	MeCN	92

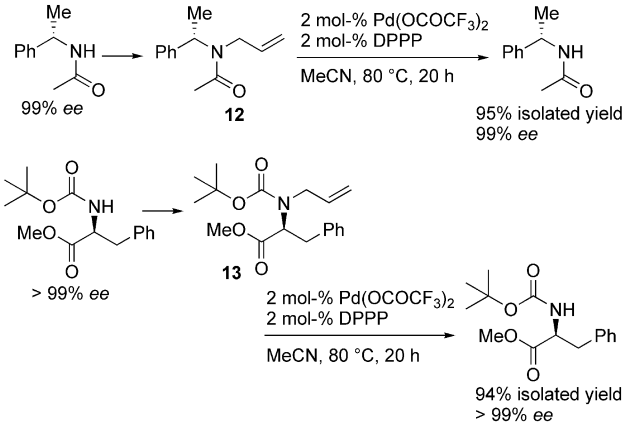
[a] The reactions were carried out on 1-mmol scale and the yield was determined by GC analysis.

Table 3. Pd-catalyzed hydrolytic deallylation from *N*-allyl amides.[a]

Entry	Substrate	Catalyst loadings [mol-%]	Time [h]	Yield [%]
1	**1**	2[b]	20	100
2	**2**	2[b]	20	99
3	**3**	2[b]	20	100
4	**4**	2[b]	20	100
5	**5**	5[c]	24	40
6	**6**	5[c]	24	53
7	**7**	5[c]	24	99
8	**8**	2[b]	24	100
9	**9**	2[b]	20	100
10	**10**	2[b]	17	100
11	**11**	2[b]	23	90

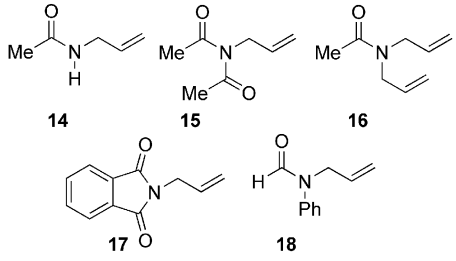
[a] The reactions were carried out on 1-mmol scale and the yield was determined by GC analysis. [b] 2 mol-% of ligand was used. [c] 5 mol-% of ligand was used.

and 11). Then optically pure compounds **12** and **13** were examined in order to examine the stability of the stereochemical center (Scheme 1). In both cases, the enantiomeric excess of the amides did not change during the reactions. In addition, Boc and methyl ester groups stayed intact under the reaction condition. A previous two-step deallylation method needs 6 N HCl under reflux conditions for 2 hours to hydrolyze an enamide.[1f] Under these conditions, Boc protecting groups or methyl ester functions will not be tolerated.



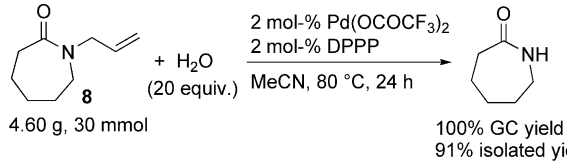
Scheme 1. Hydrolytic deallylation of optically active *N*-allyl amides.

The described catalytic hydrolysis reaction has a wide substrate scope, but there are a few limitations: *N*-allyl amides and imides of type **14**–**18** afford the desired products only in very low yields (< 20%). Substrates **14**–**16** seem to undergo further hydrolysis and give several by-products. In contrast, **17** does not undergo hydrolysis but gives an isomerized compound (1-propenyl imide, suggested by GC-MS). The substrate **18** bearing a formyl group does not react.



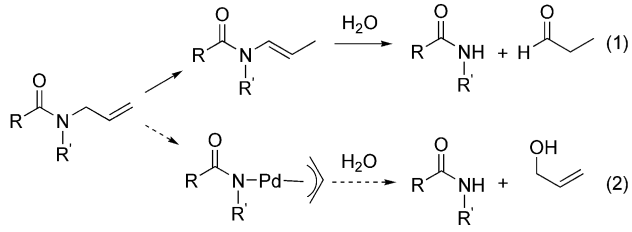
Next, a 30 mmol scale reaction with **8** was carried out with $Pd(OCOCF_3)_2$/DPPP as catalyst. The reaction proceeded smoothly to give the product in 100% GC yield and in 91% isolated yield by silica-gel column chromatography (Scheme 2).

A brief mechanistic study on the Pd-catalyzed hydrolysis reaction was carried out. Scheme 3 illustrates the possible two pathways of the reaction. Pathway (1) involves isomerization of *N*-allyl amides to give enamides and subsequent hydrolysis to amides and aldehydes, while pathway (2) gives



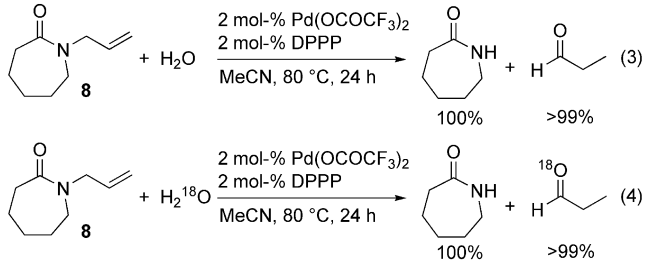
Scheme 2. Hydrolytic deallylation on 30 mmol scale.

amides and allyl alcohols via the formation of a π-allyl complex. Facile formation of π-allyl Pd complexes is generally recognized and a number of nucleophilic reagents have been developed.



Scheme 3. Possible pathways of Pd-catalyzed hydrolytic deallylation of *N*-allyl amides.

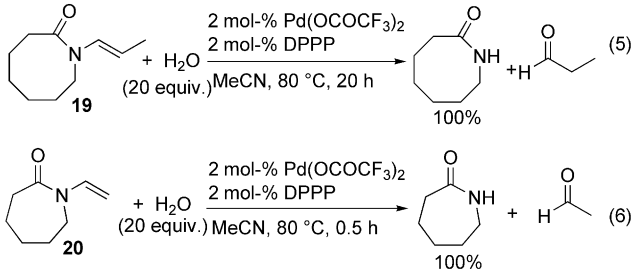
To the best of our knowledge, addition of water to π-allyl Pd complexes has not been reported except for the butadiene telomerisation which includes bis(π-allyl)Pd intermediates.[9] In addition, Zacuto et al. mentioned that Pd^0 complexes did not give any products in their preliminary investigation of deallylation.[6] In our Pd-catalyzed reaction, propanal was detected by GC and GC-MS in each run, the molar amounts of which are close to the corresponding amides (Scheme 4). Additionally, when $H_2{}^{18}O$ was used as hydrolysis reagent, ^{18}O was incorporated into the aldehyde which was confirmed by GC-MS analysis.



Scheme 4. Pd-catalyzed hydrolytic deallylation of **8** with ^{18}O-labeled water.

Based on these observations, the enamide pathway (1) seems to be plausible in this reaction like with other Rh^I-catalyzed reactions.[1b,1c,d,e,2c,6] In the case of the Rh^I-catalyzed allyl isomerization to 1-propenyl group, Rh–H species are expected to catalyze the first isomerization step. On the other hand, for the Pd-catalyzed reaction, although there are examples of Pd^{II}-catalyzed allyl amides and Pd/C-catalyzed allylamines isomerization to enamides[1f] and enamines[1h] respectively, the detail mechanism of this isomerization step is unclear and requires investigations in the future.

An intermediate enamide substrate **19** prepared from **8** with a Ru-catalyst was easily hydrolyzed under the same conditions used for the Pd-catalyzed hydrolytic deallylation of **9** [Scheme 5, Equation (5)]. In addition, the *N*-vinyl amide substrate **20**, which cannot afford π-allyl intermediate, was also hydrolyzed to give amide and acetaldehyde by use of the same Pd catalyst system [Scheme 5, Equation (6)]. We think the mechanism of hydrolysis step is similar to the Pd-complex-catalyzed vinyl ester hydrolysis,[8d] which contains side-on coordination of C=C bond of vinyl group to the Pd center. There is also the possibility of catalysis by small amounts of Brønsted acid generated by the catalyst like in other Rh^{I}-catalyzed reactions.[6] Actually, hydrolysis of **19** with 4 mol-% HCl under the similar condition gave the product quantitatively. In this case we cannot conclude which is responsible for the second hydrolysis step. For the somewhat related vinyl ether hydrolysis and alcoholysis reactions, we were able to achieve Pd-catalyzed kinetic resolution of chiral substrates with high selectivity.[8e] Therefore, although the substrates are readily hydrolyzed with Brønsted acids in this case, the Pd-catalyzed mechanism is still operative under the reaction conditions. Further studies toward elucidation of the mechanism are running.



Scheme 5. Hydrolytic deallylation of *N*-1-propenyl and *N*-vinyl amide.

Conclusions

A one-pot hydrolytic deallylation procedure for *N*-allyl amides has been realized with $Pd(OCOCF_3)_2$/DPPP catalyst system. The reaction possesses high atom efficiency and can be performed under mild conditions. Since the catalyst consists of a Pd-precursor and phosphanes, there is some potential to apply the reaction in asymmetric synthesis.

Experimental Section

Typical Procedure for the Hydrolytic Deallylation of *N*-Allyl Amides: Under N_2 atmosphere, a 20 mL Schlenk tube was charged with Pd complex (0.01 mmol), phosphane (P/Pd = 2), acetonitrile (1 mL), H_2O (360 μL), diglyme (35 μL, internal standard). The mixture was stirred at room temperature for 10 min. Then *N*-allyl amide (1 mmol) was introduced and stirring continued at 80 °C for 17–24 h. After cooling to room temperature, the yield of the product was determined by GC analysis. For the reactions of **12**, **13** and a 30 mmol scale reaction of **8**, the product was purified by silica-gel column chromatography. Enantiomeric excess of the products amides were determined by HPLC analysis (DAICEL CHIRALCEL OD-H, eluent: hexane/2-propanol = 20:1, 1 mL/min); *N*-(1-phenylethyl)acetamide [5.00 min: (*R*)-isomer, 8.15 min: (*S*)-isomer], methyl 2-*tert*-butoxycarbonylamino-3-phenylpropionate [7.83 min: (*R*)-isomer, 8.86 min: (*S*)-isomer].

Supporting Information (see also the footnote on the first page of this article): Detailed preparation and spectroscopic data of *N*-allyl amide substrates are presented.

Acknowledgments

The present work was supported by a Grant-in-Aid for Global Centers of Excellence (G-COE) program, "Kyushu University, Science for Future Molecular Systems" from the Ministry of Education, Culture, Science, Sports and Technology of Japan. This work is also supported by the New Energy and Industrial Technology Development Organization (NEDO), Industrial Technology Research Program (project ID 05A47001d). We thank Professor Katsuki and his group for permission to use their NMR equipment.

[1] a) T. W. Greene, P. G. M. Wuts, *Protective groups in organic synthesis*, 4th ed., Wiley, New York, **2006**; b) E. J. Corey, W. Suggs, *J. Org. Chem.* **1973**, *38*, 3224; c) B. Moreau, S. Lavielle, A. Marquet, *Tetrahedron Lett.* **1977**, *18*, 2591–2594; d) J. K. Stille, Y. Becker, *J. Org. Chem.* **1980**, *45*, 2139–2145; e) H. Kunz, C. Unverzagt, *J. Prakt. Chem.* **1992**, *334*, 579–583; f) S. Dallavalle, L. Merlini, *Tetrahedron Lett.* **2002**, *43*, 1835–1837; g) S. Escoubet, S. Gastaldi, M. Bertrand, *Eur. J. Org. Chem.* **2005**, 3855–3873; h) M. S. Furness, X. Zhang, A. Coop, A. E. Jacobson, R. B. Rothman, C. M. Dersch, H. Xu, F. Porreca, K. C. Rice, *J. Med. Chem.* **2000**, *43*, 3193–3196.

[2] a) F. Guibé, *Tetrahedron* **1998**, *54*, 2967–3042; b) J. Tsuji, *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 1036–1050; c) H. Kunz, H. Waldmann, *Helv. Chim. Acta* **1985**, *68*, 618–622; d) H. Waldmann, H. Kunz, *Liebigs Ann. Chem.* **1983**, 1712–1725.

[3] H. Saburi, S. Tanaka, M. Kitamura, *Angew. Chem. Int. Ed.* **2005**, *44*, 1730–1732; S. Tanaka, H. Saburi, M. Kitamura, *Adv. Synth. Catal.* **2006**, *348*, 375–378; S. Tanaka, H. Saburi, T. Murase, Y. Ishibashi, M. Kitamura, *J. Organomet. Chem.* **2007**, *692*, 295–298; S. Tanaka, T. Hirakawa, K. Oishi, Y. Hayakawa, M. Kitamura, *Tetrahedron Lett.* **2007**, *48*, 7320–7322.

[4] T. Fukuyama, A. A. Laird, C. A. Schmidt, *Tetrahedron Lett.* **1984**, *25*, 4709–4712.

[5] a) G. Cainelli, D. Giacomini, P. Galletti, *Synthesis* **2000**, 289–294; b) O. Kanno, M. Miyauchi, I. Kawamoto, *Heterocycles* **2000**, 289–294; c) B. Alcaide, P. Almendros, J. M. Alonso, *Tetrahedron Lett.* **2003**, *44*, 8693–8695; d) B. Alcaide, P. Almendros, J. M. Alonso, *Chem. Eur. J.* **2006**, *12*, 2874–2879.

[6] M. J. Zacuto, F. Xu, *J. Org. Chem.* **2007**, *72*, 6298–6300.

[7] V. Cadierno, J. Gimeno, N. Nebra, *Chem. Eur. J.* **2007**, *13*, 6590–6594.

[8] a) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936–938; b) M. Tokunaga, Y. Wakatsuki, *Angew. Chem. Int. Ed.* **1998**, *37*, 2867–2869; c) M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi, Y. Wakatsuki, *J. Am. Chem. Soc.* **2001**, *123*, 11917–11924; d) H. Aoyama, M. Tokunaga, S. Hiraiwa, Y. Shirogane, Y. Obora, Y. Tsuji, *Org. Lett.* **2004**, *6*, 509–512; e) H. Aoyama, M. Tokunaga, J. Kiyosu, T. Iwasawa, Y. Obora, Y. Tsuji, *J. Am. Chem. Soc.* **2005**, *127*, 10474–10475; f) M. Tokunaga, J. Kiyosu, Y. Obora, Y. Tsuji, *J. Am. Chem. Soc.* **2006**, *128*, 4481–4486; g) M. Tokunaga, H. Aoyama, J. Kiyosu, Y. Shirogane, T. Iwasawa, Y. Obora, Y. Tsuji, *J. Organomet. Chem.* **2007**, *692*, 472–480.

[9] K. E. Atkins, W. E. Walker, R. M. Manyik, *J. Chem. Soc., Chem. Commun.* **1971**, 330.

Received: August 6, 2008
Published Online: September 16, 2008

