

293(2) K. The compound crystallized in the space group $P2_1/n$, monoclinic, dimensions $0.35 \times 0.10 \times 0.08$ mm, $a = 24.246(5)$, $b = 9.5182(19)$, $c = 24.685(8)$ Å, $\alpha = 90.96(3)^\circ$, $V = 5696(2)$ Å³, $Z = 4$, $\rho_{\text{calc}} = 1.153$ Mg m⁻³, $\lambda = 0.71073$ Å, $\mu(\text{MoK}\alpha) = 1.463$ mm⁻¹, $F(000) = 1992$. A total of 34441 reflections were collected in the range of $1.65^\circ \leq \theta \leq 28.02^\circ$, of which 13040 were unique reflections and 4517 with $I \geq 2\sigma(I)$ were collected for the analysis. The structure was solved by full-matrix least-squares on F^2 values (SHELX-97). Non-hydrogen atoms (excluding disordered and solvent atoms) were refined anisotropically. The disordered atoms were modeled in 50% SOF. Hydrogen atoms were fixed at calculated positions and refined by using a riding mode. The final indices were $R1 = 0.0561$, $Rw2 = 0.1149$ with goodness-of-fit = 1.023. CCDC-168798 (**1**) and CCDC-168799 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[7] Thermal analyses were carried out using a TA-SDT 2960 apparatus at a heating rate of 5 K min⁻¹ from 20 to 1000 °C under a flux of nitrogen: 6.8505 mg of the sample **1** and 11.9348 mg **2** were used for the measurement.

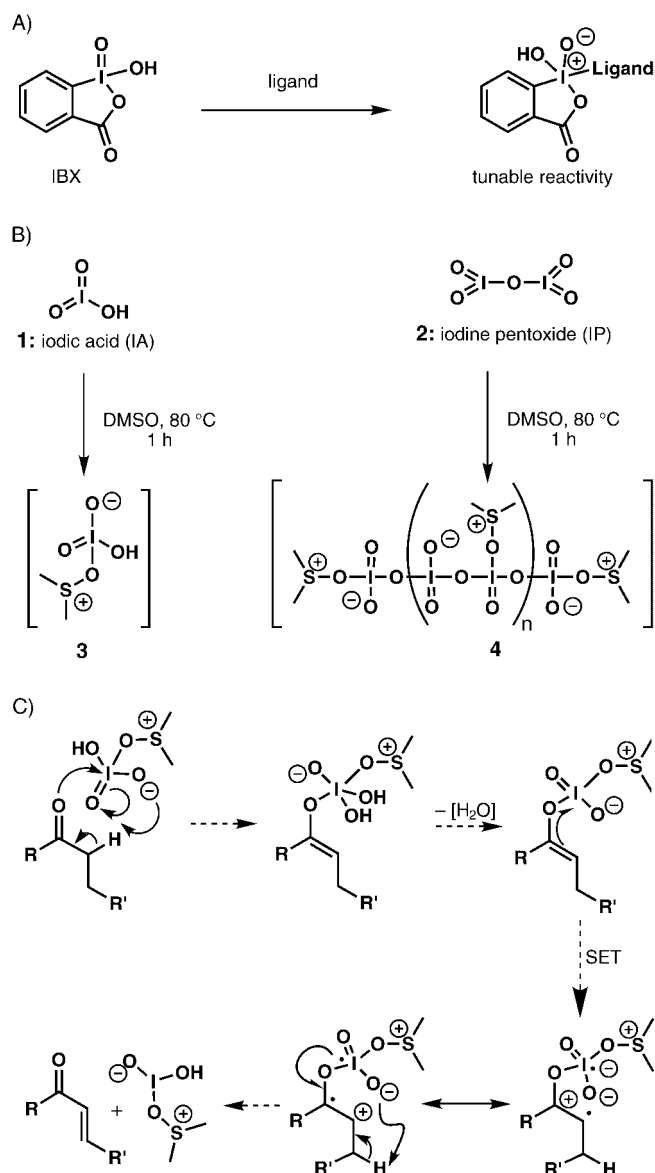
[8] D. M. L. Goodgame, D. A. Grachvogel, D. J. Williams, *Angew. Chem.* **1999**, *111*, 1217–219; *Angew. Chem. Int. Ed.* **1999**, *38*, 153–156.

HIO₃ and I₂O₅: Mild and Selective Alternative Reagents to IBX for the Dehydrogenation of Aldehydes and Ketones**

K. C. Nicolaou,* Tamsyn Montagnon, and Phil S. Baran

Although the chemistry of iodine(III) and iodine(VII) reagents has been extensively explored,^[1] that of the iodine(V) manifold, which includes reagents such as 1-hydroxy-1,2-benziodoxal-3(1H)-one-1-oxide (IBX) and Dess–Martin periodinane (DMP), remained until recently almost entirely relegated to being a source of reliable agents for the simple oxidation of alcohols and for a number of closely related processes.^[2] However, a recent discovery that stems from endeavors in total synthesis in our laboratories^[3] has opened the door to the development of a number of novel iodine(V)-mediated reactions.^[4–11] Furthermore, detailed mechanistic

studies into one of these processes, the IBX-mediated dehydrogenation of ketones and aldehydes,^[10, 11] led to the recognition of the importance of the ligand appended to the iodine nucleus in this and other SET-based process (Scheme 1 A).^[7] Armed with this information, we were able to tune the reactivity at the iodine nucleus by using a variety of *N*-oxide ligands, and hence developed a mild room-temperature variant of the original IBX dehydrogenation with expanded functional group tolerance.^[12] With such dramatic changes in reactivity patterns on changing the ligand from THF^[7, 8] or DMSO^[10, 11] to an *N*-oxide,^[12, 13] we began to question the role of all the substituents on the iodine nucleus, including the aromatic core. Herein we report initial results that probe the latter question and provide us with a number of economic, commercially available, and safe iodine(V) dehydrogenation agents whose structures contain no aromatic moiety.



Scheme 1. A) The tunable reactivity of IBX by using different ligands prompted the investigation of the role of the aromatic moiety. B) This led to development of **3** and **4** as dehydrogenating agents. C) Postulated mechanism of action.

[*] Prof. Dr. K. C. Nicolaou, Dr. T. Montagnon, Dr. P. S. Baran
Department of Chemistry and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

[**] We thank Dr. D. H. Huang, Dr. G. Suizdak, and Dr. Raj Chahda for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, fellowships from GlaxoWellcome (T.M.) and the National Science Foundation (P.S.B.), and grants from Amgen, Array Biopharma, Boehringer-Ingelheim, Glaxo, Hoffmann-LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

To determine the role of the aryl moiety in the reactivity of IBX, we evaluated the most simple iodine(V)-based reagents: HIO_3 (**1**, iodic acid, IA) and its anhydride I_2O_5 (**2**, iodine pentoxide, IP) (Scheme 1 B). Both were efficient reagents for the mild and chemoselective dehydrogenation of carbonyl compounds. Despite their extensive use in industry^[14] and their commercial availability,^[15] IA and IP have rarely been employed in organic synthesis. Their industrial applications and studies conducted at elevated temperatures^[16] strongly suggest that these agents are particularly stable oxidants. This feature is perhaps related to the stabilization attained through the extensive secondary bonding networks present in the solids and, at least partially, maintained in solution.^[17] There is, therefore, no indication that they pose the same detonation risk that is claimed for IBX.^[18] Our first exploration of this chemistry probed the ability of these simple reagents to oxidize alcohols to carbonyl-containing compounds; we found

that alcohol substrates are inert to these oxidants. In light of the results elaborated below, initial coordination of the substrate is unlikely to be responsible for this lack of reactivity and, therefore, a possible explanation could be that the oxide ligand is less basic than the one on IBX. We reasoned that dehydrogenation might still be feasible (for a mechanistic rationale, see Scheme 1 C), and by analogy to our studies with IBX,^[11] we prepared the DMSO complexes of IA and IP (Scheme 1 B, **3** and **4**, respectively).

Gratifyingly, the IA·DMSO (**3**) and IP·DMSO (**4**) complexes are remarkably mild and efficient oxidants, and can be used for dehydrogenation of both aldehydes and ketones (Table 1). Although equally efficient, we favored the use of IA in these reactions over its more expensive anhydride IP. Moreover, since the oxidation reactions tend to produce varying amounts of detrimental iodine as a by-product, cyclohexene was added as a cosolvent. Under optimal

Table 1. Facile dehydrogenation of ketones and aldehydes using HIO_3 (IA) and I_2O_5 (IP).^[a]

Entry	Substrate	Product	IA [equiv]	Temperature	Time [h]	Yield [%] ^[b]
1			1.8	50 °C	18	88
2			1.1	50 °C	8	95
3			1.2	50 °C	4	88
4			1.7	50 °C	6	78
5			1.7	50 °C	6	82 ^[c]
6			2.5	65 °C	18	82
7			1.7	45 °C	6	74
8			1.4	50 °C	6	90
9			1.5	50 °C	12	92
10			1.2	50 °C	12	77

[a] Reactions were carried out on a 0.1–1.5-mmol scale in DMSO. [b] Yield of isolated chromatographically pure compound. [c] Starting material is commercially available as a mixture of regioisomers; products were separated by chromatography.

conditions, 1.3–2.5 equivalents of **3** (1M solution in DMSO, prepared by heating a solution of IA in DMSO at 80 °C for 1 h) and cyclohexene (0.25 mLmmol of substrate) are used. The reaction mixture, which included a further dilution with DMSO (1.0 mLmmol of substrate), was heated in a sealed tube at 45–65 °C for 5–12 h, with light excluded from the vessel. Standard reagent grade DMSO and cyclohexene were used, and the reaction was impervious to moisture or air. The workup was operationally very simple and provided pure products after flash column chromatography.

The scope of the reaction appears to be similar to the IBX-mediated dehydrogenation.^[10, 11] One difference, however, was the remarkable ease with which the indanone nucleus could be oxidized (Table 1, entries 4 and 5) in high yields. This particular transformation has challenged the more traditional dehydrogenation techniques, which give poor yields and often unwanted by-products.^[19] Mindful of the challenges associated in some instances with the preparation of simple enones on a large scale^[20] in terms of expense and practicality, we tested the present method in this arena. Cyclopentanone was cheaply and efficiently converted into its enone in 74 % yield on a 0.15-mole scale (Table 1, entry 7). We took advantage of the inertness of alcohols towards **3** and selectively dehydrogenated a ketone in the presence of an unprotected alcohol (Table 1, entry 9). To confirm that this result was not related to the steric environment of the alcohol in this example, an intermolecular competition experiment was undertaken in which *tert*-butylcyclohexanone was smoothly converted into *tert*-butylcyclohexenone in the presence of one equivalent of a primary alcohol (Scheme 2). No aldehyde was observed in the reaction (monitored by means of ¹H NMR spectroscopy).

Table 2. Selected data for **5** and **6** (determined by means of NOE and ROESY NMR spectroscopic analysis).

5: Bright yellow oil; R_f = 0.24 (silica gel, hexane/diethyl ether 9:1); IR (film): $\tilde{\nu}_{\max}$ = 3082, 2923, 2861, 1714, 1580, 1542, 1484, 1379 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.58 (d, J = 6.2 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 5.91 (d, J = 6.2 Hz, 1H), 2.26 (s, 3H); ¹³C NMR (150 MHz, CDCl₃): δ = 195.9, 146.0, 145.0, 136.4, 133.9, 127.0, 116.1, 16.6; high-resolution MS (matrix-assisted laser desorption/ionization (MALDI)): calcd for C₁₀H₇OBrNa [M +Na⁺]: 244.9572; found: 245.0455; MS (electrospray ionization (ESI)): [M +H⁺]: 223.

6: Bright yellow oil; R_f = 0.56 [silica gel, hexane/diethyl ether 9:1]; IR (film): $\tilde{\nu}_{\max}$ = 2921, 2852, 1702, 1659, 1644, 1538, 1453, 1385 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.60 (d, J = 5.9 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 5.90 (d, J = 5.9 Hz, 1H), 2.44 (s, 3H); ¹³C NMR (150 MHz, CDCl₃): δ = 198.8, 147.7, 144.5, 136.6, 136.2, 128.6, 127.9, 114.3, 16.6; HRMS (MALDI) calcd for C₁₀H₇OBrNa [M +Na⁺]: 244.9572; found: 245.0448; MS (ESI): [M +H⁺]: 223.

To improve our understanding of the nature of these iodine(v)·DMSO complexes, we prepared crystalline **4** by lyophilization of a solution of **4** in DMSO (1.2M).^[21] The ORTEP representation (Figure 1), obtained from X-ray crystallographic analysis of this complex, shows that **4** self-assembles into a remarkable helix in the solid state. Within the “grooves” of this helix, additional molecules of DMSO are bound to the iodine nuclei by secondary bonds. Based on the observed bond lengths for this assembly, we believe that the complex in solution can be depicted as shown in Scheme 1.

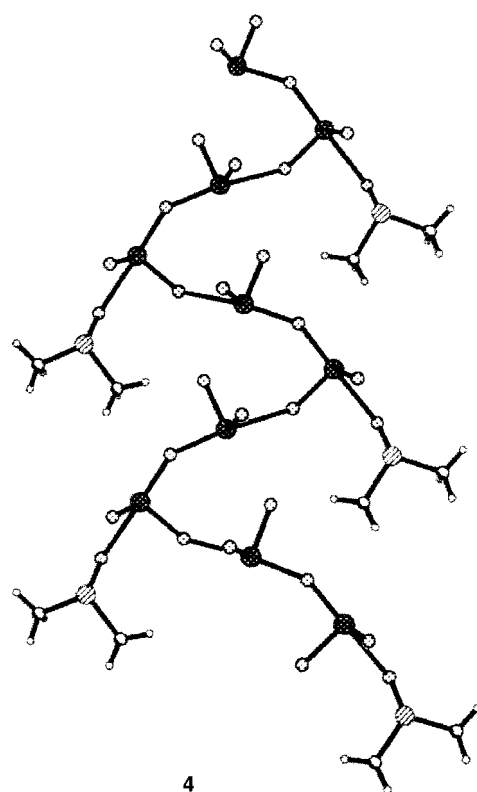
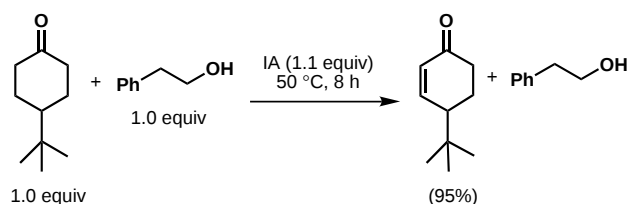


Figure 1. ORTEP representation of the helical IPwDMSO complex (**4**).



Scheme 2. Unprotected alcohols are inert to the reaction conditions utilized in this procedure.

In conclusion, we have demonstrated the unique mild and efficient nature of HIO₃ and its anhydride I₂O₅ as commercially available, more atom-efficient, and safer alternatives to IBX for the dehydrogenation of carbonyl compounds. Furthermore, these IBX surrogates are highly chemoselective, and effect smooth dehydrogenations at 45–65 °C in the presence of a variety of sensitive functionalities, including unprotected alcohols. We have also shown that the procedure developed here is amenable to large-scale operations, with high efficiency and cost effectiveness. Our investigations now center on exploring other possible transformations of these versatile reagents and their complexes with a variety of ligands.

Received: December 21, 2001 [Z18429]

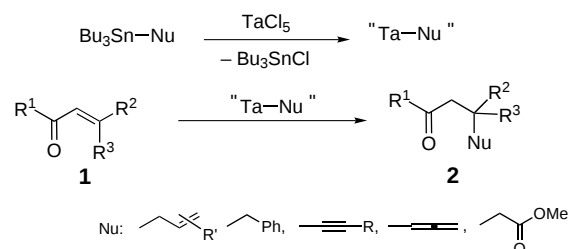
- [1] A. Vargolis, *Hypervalent Iodine in Organic Synthesis*, Academic Press, London, **1997**; T. Wirth, U. H. Hirt, *Synthesis* **1999**, 1271.
- [2] DMP: D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277; IBX: M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019; for a review, see: S. S. Chaudhari, *Synlett* **2000**, 278.

- [3] K. C. Nicolaou, P. S. Baran, *Angew. Chem.* **2002**, *114*, in press; *Angew. Chem. Int. Ed.* **2002**, *41*, in press.
- [4] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, K. Sugita, *J. Am. Chem. Soc.*, in press.
- [5] K. C. Nicolaou, Y.-L. Zhong, P. B. Baran, *Angew. Chem.* **2000**, *112*, 636; *Angew. Chem. Int. Ed.* **2000**, *39*, 622; Corrigendum: K. C. Nicolaou, Y.-L. Zhong, P. B. Baran, *Angew. Chem.* **2000**, *112*, 1592; *Angew. Chem. Int. Ed.* **2000**, *39*, 1532.
- [6] K. C. Nicolaou, K. Sugita, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.*, in press.
- [7] K. C. Nicolaou, P. S. Baran, R. Kranich, Y.-L. Zhong, K. Sugita, N. Zou, *Angew. Chem.* **2001**, *113*, 208; *Angew. Chem. Int. Ed.* **2001**, *40*, 202.
- [8] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich, J. A. Vega, *J. Am. Chem. Soc.*, in press.
- [9] a) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, *Angew. Chem.* **2000**, *112*, 636; *Angew. Chem. Int. Ed.* **2000**, *39*, 625; b) K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, J. A. Vega, *Angew. Chem.* **2000**, *112*, 2625; *Angew. Chem. Int. Ed.* **2000**, *39*, 2525.
- [10] K. C. Nicolaou, T. Montagnon, Y.-L. Zhong, P. S. Baran, *J. Am. Chem. Soc.*, in press.
- [11] K. C. Nicolaou, Y.-L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2000**, *122*, 7596.
- [12] K. C. Nicolaou, T. Montagnon, P. S. Baran, *Angew. Chem.* **2002**, *114*, 1035; *Angew. Chem. Int. Ed.* **2002**, *41*, 993.
- [13] K. C. Nicolaou, T. Montagnon, D. L. F. Gray, S. T. Harrison, *Angew. Chem.* **2002**, *114*, 1038; *Angew. Chem. Int. Ed.* **2002**, *41*, 996.
- [14] A search with SciFinder Scholar uncovered a plethora of current industrial applications for these iodine oxides; for selected examples, see: a) U. Hiroto, N. Keiji, O. Katsumi, Patent no. JP 06040710, **1994** [*Chem. Abstr.* **1994**, *120*, 326849]; b) T. Ueno, H. Shiraishi, T. Iwayanagi, S. Nonogaki, *J. Electrochem. Soc.* **1985**, *132*, 1168.
- [15] Iodic acid is available for about 25 cents per gram from ABCR GmbH and Co. and iodine pentoxide is available for about 75 cents per gram from Fluka. Both are also available from Aldrich.
- [16] IP is purified as white crystal by sublimation at 250 °C: K. Selte, A. Kjekshus, *Acta Chem. Scand.* **1968**, *22*, 3309. There are a number of papers that deal with the thermal chemistry of these iodine oxides. The most recent advocates the thermolysis reaction of IP as a "first chemistry lesson" for school children, which attests to the confidence that chemists have in its predictable behavior at elevated temperatures: J. Kuhmstedt, *Prax. Naturwiss. Chem.* **1999**, *48*, 13.
- [17] K. Selte, A. Kjekshus, *Acta Chem. Scand.* **1970**, *24*, 1912.
- [18] IBX was reported to be explosive under excessive heating and also upon impact: J. B. Plumb, P. J. Harper, *Chem. Eng. News* **1990**, *68*(29), 3; these reports may be related to the method used to synthesize the IBX: D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.
- [19] Selected examples: halogenation/dehalogenation: D. L. Boger, Y. Zhu, *J. Org. Chem.* **1994**, *59*, 12; R. J. Heffner, M. M. Joulie, *Synth. Commun.* **1991**, *21*, 2231; DDQ oxidation: J. T. K. Angandi, K. G. S. Rao, *Indian J. Chem. Sect. B* **1983**, *22*, 735; selenium-based reagents: M. Fukuoka, *Chem. Pharm. Bull.* **1978**, *26*, 2365.
- [20] The conversion of cyclopentanone into cyclopentenone is considered to be challenging to industry and prompted www.innocentive.com, an Eli Lilly business venture, to post a \$25000 reward for cheap novel methods for this reaction.
- [21] CCDC-176208 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Generation of Organotantalum Reagents and Conjugate Addition to Enones**

Ikuya Shibata,* Takeyoshi Kano, Nobuaki Kanazawa, Shoji Fukuoka, and Akio Baba*

Organotin compounds are good precursors for generating active organometallic agents through transmetalation.^[1, 2] For example, active allylic titanium complexes generated from allylic tin complexes have performed effective allylation of carbonyl compounds.^[1] In contrast, generation and synthetic use of similar early transition metal complexes such as tantalum reagents^[3] have not been reported so far, although Ta–C bonds are known to be moderately reactive to electrophiles.^[4, 5] We report here on the preparation of active tantalum reagents by the transmetalation of organotin compounds with tantalum(v) chloride. Of particular interest is that certain tantalum reagents promote the conjugate allylation of enones (Scheme 1).



Scheme 1. Generation of an active tantalum–nucleophile complex and subsequent addition to an enone.

Compared with the direct allylation of carbonyl groups, little has been reported on the selective conjugate allylation of enones.^[6] The only choice for this purpose has been the Hosomi–Sakurai reaction (allylsilane and TiCl_4).^[7a] Later, modified reagents such as allylbarium^[7b] and allylcopper^[7c] were developed to avoid strong acidic conditions. However, with these modified reagents the allylation of acyclic enones is far more difficult than that of cyclic ones. The present system could be the method of choice for conjugate addition of allylic nucleophiles including sterically hindered ones to enones.^[8]

The results of the conjugate allylation of enones, both acyclic and cyclic substrates, are given in Table 1. Under the conditions described in the Experimental Section, benzalacetone (**1a**) was allylated to give the conjugate adduct **2a** in 91% yield (entry 1, Table 1). The yield decreased to 50%

[*] Dr. I. Shibata, Prof. Dr. A. Baba, T. Kano, N. Kanazawa, S. Fukuoka
Department of Molecular Chemistry & Frontier Research Center
Graduate School of Engineering, Osaka University
2–1 Yamadaoka, Suita, Osaka, 565-0871 (Japan)
Fax: (+81) 6-6879-7387
E-mail: shibata@ap.chem.eng.osaka-u.ac.jp

[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of the Japanese Government. We thank Mr. H. Moriguchi, Faculty of Engineering, Osaka University, for assistance in obtaining mass spectra.

Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.