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Published on Web 04/29/2005

One-Pot Synthesis of Metalated Pyridines from Two Acetylenes, a Nitrile, and a Titanium(II) Alkoxide

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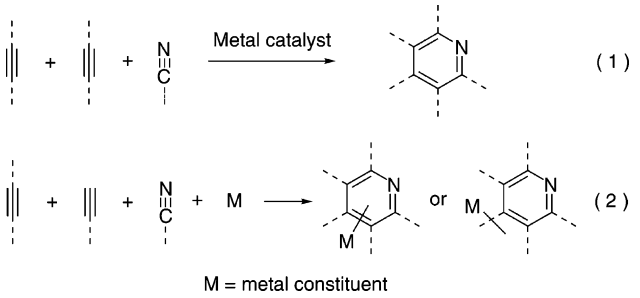
Abstract: Four-component coupling process involving two acetylenes, a nitrile, and a divalent titanium alkoxide reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, directly yielded titanated pyridines in a highly selective manner. The reaction can be classified into four categories: (i) a combination of an internal acetylene, a terminal acetylene, sulfonylnitrile, and the titanium reagent to yield α-titanated pyridines, (ii) a combination of an internal acetylene, a (sulfonylamino)acetylene, a nitrile, and the titanium reagent to yield alternative α-titanated pyridines, (iii) a combination of an internal acetylene, a (sulfonylamino)acetylene, a nitrile, and the titanium reagent to yield titanated aminopyridines, and (iv) a combination of an acetylenic amide, a terminal acetylene, a nitrile, and the titanium reagent to yield pyridineamides with their side chain titanated. Some of these reactions enabled virtually completely regioselective coupling of two different, unsymmetrical acetylenes and a nitrile to form a single pyridine. Synthetic applications of these reactions have been illustrated in the preparation of optically active pyridines and medicinally useful compounds.

Introduction

Pyridines are a most fundamental heterocyclic compound, and numerous methods for their preparation have been developed.[1] Among these methods, Reppe-type reactions, that is, the cyclization of two molecules of acetylenes and one molecule of nitrile as formulated in eq 1, attract much attention,[2,3] because this protocol is conceptually straightforward, requires simple starting materials, and provides synthetic versatility. However, one problem associated with this transformation is that of regioselectivity. Completely organized assembly of two different unsymmetrical acetylenes and one nitrile, giving a single pyridine, is an ideal goal of this transformation and is essential also from the practical point of view.[3−5] In addition, in consideration of the pivotal role of organometallic compounds in current organic synthesis, we conceived that a direct preparation of a pyridylmetal



reagent,[1c] a new transformation as formulated in eq 2, would be an attractive alternative of eq 1. In this article, we describe

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(1) For reviews, see: (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 2. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491−2515. (c) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059−4090. (d) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043−6061. (e) Katritzky, A. R., Ed. *Chem. Rev.* **2004**, *104*, 2127−2812.

(2) For reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (b) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787−3802. (c) Bönnemann, H.; Brijoux, W. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 1, pp 114−135. (d) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 741−770. (e) Chelucci, G. *Tetrahedron: Asymmetry* **1995**, *6*, 811−826. (f) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1129−1162. (g) Bönnemann, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 248−262. (h) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−556.

(3) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Chem. Commun.* **1973**, 280. Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Dalton Trans.* **1978**, 1278−1282. There had been no reports on the selective cyclotrimerization of two different, unsymmetrical acetylenes and a nitrile before we and others reported such examples (see refs 4 and 5). For recent reports, which deal with cyclotrimerization of the same (ref 3a−h), symmetrical (ref 3i), or tethered (ref 3j−p) substrates, see: (a) Bianchini, C.; Meli, A.; Peruzzini, M.; Vacca, A.; Vizza, F. *Organometallics* **1991**, *10*, 645−651. (b) Smith, D. P.; Strickler, J. R.; Gray, S. D.; Bruck, W. A.; Holmes, R. S.; Wigley, D. E. *Organometallics* **1992**, *11*, 1275−1288. (c) Viljoen J. S.; du Plessis, J. A. K. *J. Mol. Catal.* **1993**, *79*, 75−84. (d) Diversi, P.; Ermini, L.; Ingrosso, G.; Lucherini, A. *J. Organomet. Chem.* **1993**, *447*, 291−298. (e) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911−2924. (f) Jerome, K. S.; Parsons, E. J. *Organometallics* **1993**, *12*, 2991−2993. (g) Heller, B.; Oehme, G. *J. Chem. Soc., Chem. Commun.* **1995**, 179−180. (h) Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131−3133. (i) Takahashi, T.; Tsai, F.-Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994−4995. (j) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487−489. (k) Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett.* **1995**, 851−852. (l) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **1997**, *62*, 4189−4192. (m) Varela, J. A.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **1998**, *120*, 12147−12148. (n) Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **1999**, *1*, 2141−2143. (o) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2001**, 1102−1103. (p) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189−6190.

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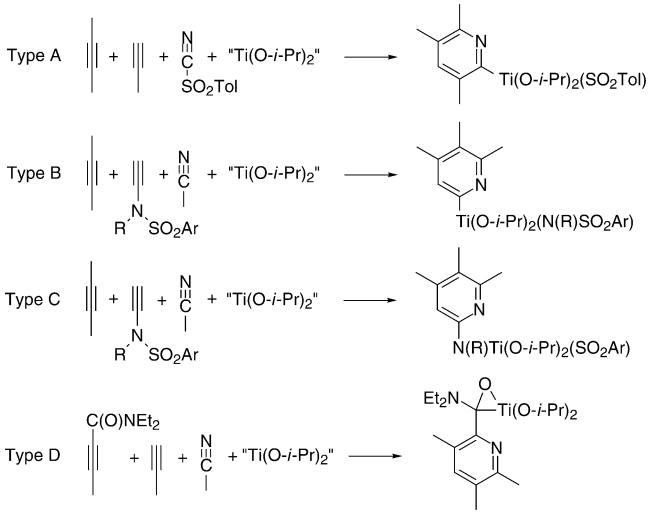
Scheme 1. Formulation of New Synthesis of Metalated Pyridines



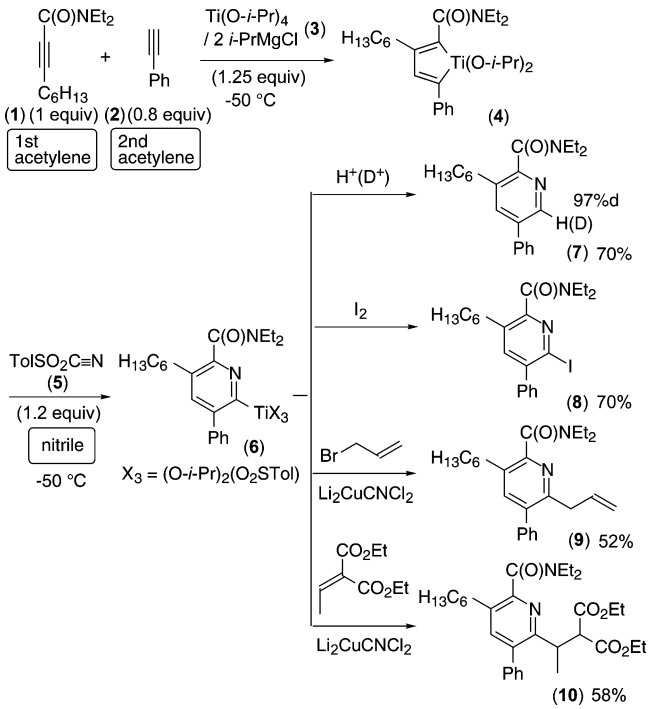
new syntheses of metalated pyridines according to eq 2, where solutions to the above two issues are presented.

The transformation of eq 2 described in this article will be divided into four categories, types A−D, as shown in Scheme 1. These transformations always involve a combination of acetylenes, a nitrile, and a low-valent titanium reagent under similar reaction conditions, but the products cover a wide range of metalated pyridines, which will be discussed in order.

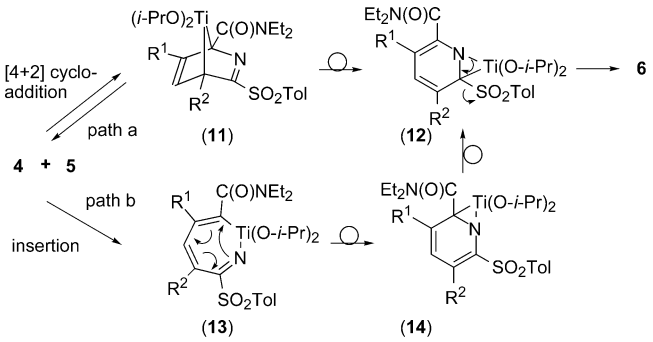
Results and Discussion

Type-A Preparation of Pyridines from Two Acetylenes and a Nitrile Having a Leaving Group. Two different, unsymmetrical acetylenes **1** and **2** (as the first and second acetylenes) were first treated with a divalent titanium alkoxide reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl (**3**),[6,7] at −50 °C to generate dialkoxytitanacyclopentadienes **4** in a highly regioselective manner according to the previously published protocol (Scheme 2).[8] Then, *p*-toluenesulfonylnitrile (**5**, TolSO$_2$− = *p*-MeC$_6$H$_4$SO$_2$−)[9] was added as the nitrile component. After hydrolytic workup of the reaction mixture, pyridine **7** was obtained as a single isomer, showing that the regioselective uptake of the nitrile into the titanacyclopentadiene **4** took place. More importantly, deuteriolysis gave deuterated counterpart **7**d with high deuterium incorporation at the depicted position, confirming the presence of pyridyltitanium compounds **6** before aqueous workup (type A in Scheme 1). The pyridylmetal species **6**, in fact, enabled subsequent transformations:[10,11] on treatment of **6** with iodine, allyl bromide, or ethylidenemalonate-furnished iodopyridine **8** or homologated aromatic compounds **9** and **10** (Scheme 2). Thus, an advantageous feature of the formation of titanated pyridines **6** over the conventional metal-catalyzed pyridine synthesis (eq 1) was demonstrated.

Scheme 2. Preparation of Metalated Pyridines



Scheme 3. Proposed Reaction Course



The reaction course may be explained by either path a or b in Scheme 3.[12] Path a involves the [4 + 2]-type cycloaddition of titanacycle **4** and nitrile **5**. The carbon−titanium bond in the resultant titanacycle **11** rearranges to a suitable position to eliminate the sulfonyl group (**12**) to complete the aromatization (→**6**). Alternatively, in path b, regioselective insertion of nitrile **5** to the titanacycle **4** followed by electrocyclization of **13** yielded **14**, from which the elimination of the sulfonyl group took place via **12** to furnish the same final product **6** as in path a. In any event, the high regioselectivity of the cycloaddition (in path a) or that of the insertion reaction (in path b), most likely controlled by the amide group in **4**, is the key to the selective formation of single metalated pyridine **6**.

More examples of the present synthesis of metalated pyridines achieving the coupling of two different unsymmetrical acetyl-

(4) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **2002**, *124*, 3518−3519. Portions of type-A and type-D reactions in Scheme 1 have been reported in this communication.
(5) Takahashi, T.; Tsai, F.-Y.; Li. Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc*. **2002**, *124*, 5059−5067.
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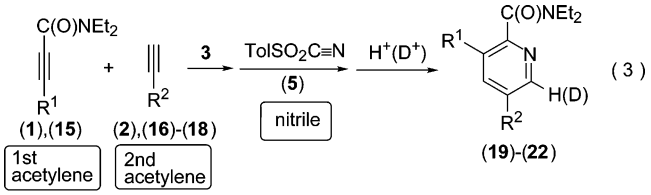
(8) Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem*. **1999**, *71*, 1511−1519. Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **1999**, *121*, 1245−1255. Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **1999**, *121*, 7342−7344. Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett*. **2000**, *2*, 3481−3484.
(9) *p*-Toluenesulfonylnitrile is commercially available.
(10) For synthetic application of organotitanium compounds, see: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139−172. Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 1994; pp 195−282.
(11) Urabe, H.; Hamada, T.; Sato, F. *J. Am. Chem. Soc*. **1999**, *121*, 2931−2932.
(12) However, the intermediates in this scheme so far remain unidentified.

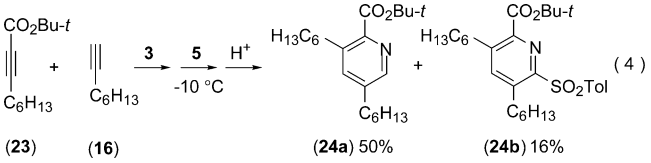
enes and a nitrile are shown in eq 3 in order to reinforce its generality. Various acetylenic amides (as the first acetylene) and the second acetylenes afforded the desired products **19**−**22** under the same reaction conditions as Scheme 2. In all cases, the presence of the intermediate metalated pyridines was guaranteed by deuteriolysis.



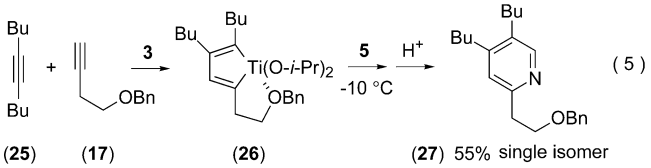
1st acetylene		2nd acetylene		Product		
R^1		R^2			Yield (%)[a]	D (%)
C_6H_{13}	**1**	C_6H_{13}	**16**	**19**	62-63[b]	96
C_6H_{13}	**1**	$BnO(CH_2)_2$-	**17**	**20**	68	98
C_6H_{13}	**1**	$SiMe_3$	**18**	**21**	55	97
Ph	**15**	Ph	**2**	**22**	67	96

[a]Based on the 2nd acetylene. [b]Depending on reaction scale. See the experimental section.

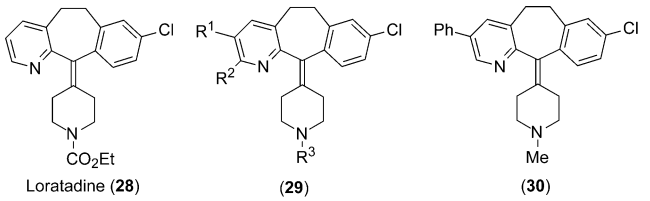
In place of the acetylenic amides, acetylenic ester **23** afforded the expected pyridine **24a** as a single isomer as well after hydrolysis (eq 4) yet accompanied with a small amount of



sulfonylated pyridine **24b**. The latter product **24b** may arise from aerial oxidation of dihydropyridines produced by the hydrolysis of the intermediate titanium species such as **11**, **12**, **14**, etc. in Scheme 3 before elimination of the sulfonyl group.[13] Thus, this observation implies that the reaction most likely proceeds via the proposed path depicted in Scheme 3. When the reaction was started with dialkylacetylene **25** (eq 5), the regiochemical control of the nitrile uptake appears to be problematic, because both α-substituents of the intermediate titanacyclopentadiene **26** are alkyl groups that are hardly discriminated. However, eq 5 highlighted a device to secure the regioselective incorporation of the nitrile, where the neighboring benzyl ether in the side chain apparently controls the direction of the incoming nitrile to achieve the selective production of **27**.[14]



The quick assembly of acetylenes and nitriles to yield pyridine derivatives as shown above should be particularly useful for the construction of polysubstituted pyridines often found in medicinally important substances. Loratadine (**28**) is an anti-



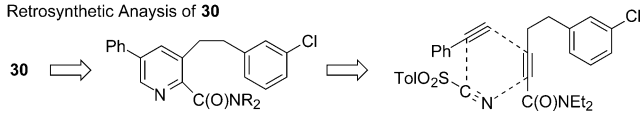
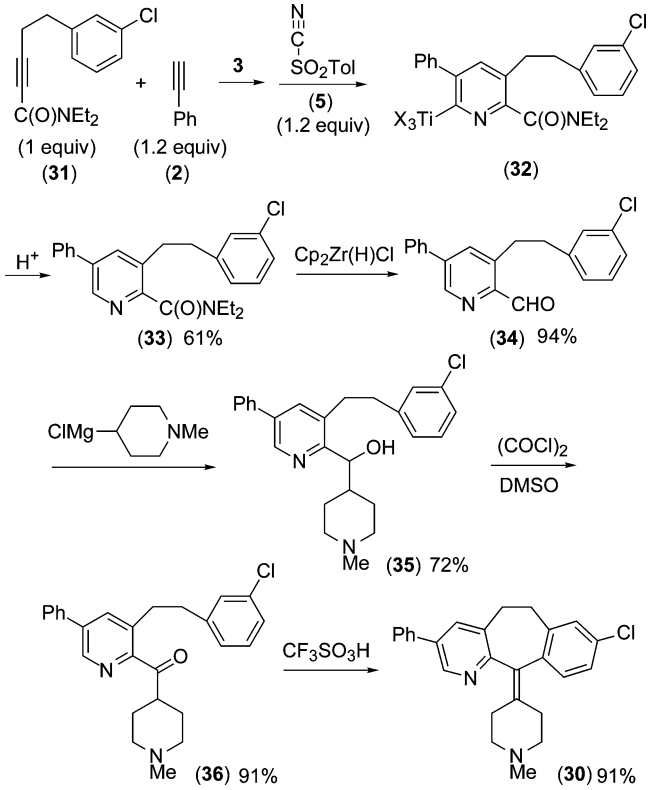


Figure 1. Benzocyclohepatapyridines.

Scheme 4. Synthesis of **30**



allergic substance[15a] and is actually sold under the commercial name Claritin (Figure 1). Its substituted derivatives having a common structure of benzocycloheptapyridine **29** have been synthesized and were subjected to medicinal evaluation.[15] A derivative **30**[15b] was chosen as a representative synthetic target to demonstrate the utility of the aforementioned coupling of acetylenes and a nitrile (retrosynthetic analysis, Figure 1).

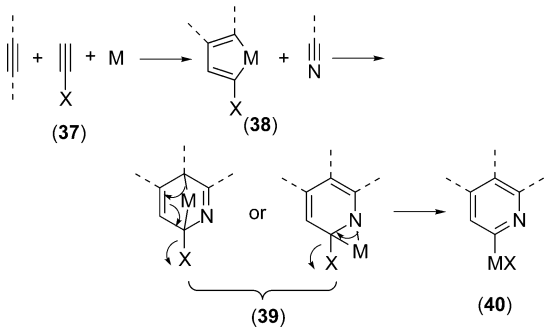
Acetylenic amide **31** equipped with a chlorophenyl group, phenylacetylene (**2**), and nitrile **5** were submitted to the titanium-mediated coupling reaction, which proceeded without difficulty to give **33** after hydrolytic workup (Scheme 4). A few additional steps consisting of (i) a functional group transformation (**33**→

(13) When the reaction was quenched at a lower temperature (−50 °C), sulfonylpyridine **24b** became a major constituent (**24b** and **24a** in 37 and 28% yields, respectively).

(14) For additional control experiments and discussion, see the Experimental Section.

(15) (a) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem.* **1989**, *54*, 2242−2244. (b) Wong, J. K.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Anthes, J. C.; Billah, M. M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1073−1078. (c) Njoroge, F. G.; et al. *J. Med. Chem.* **1997**, *40*, 4290−4301. (d) Njoroge, F. G.; et al. *J. Med. Chem.* **1998**, *41*, 4890−4902. (e) Njoroge, F. G.; Vibulbhan, B.; Pinto, P.; Chan, T.-M.; Osterman, R.; Remiszewski, S.; Rosario, J. D.; Doll, R.; Girijavallabhan, V.; Ganguly, A. K. *J. Org. Chem.* **1998**, *63*, 445−451. (f) Cooper, A. B.; Strickland, C. L.; Wang, J.; Desai, J.; Kirschmeier, P.; Patton, R.; Bishop, W. R.; Weber, P. C.; Girijavallabhan, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 601−605.

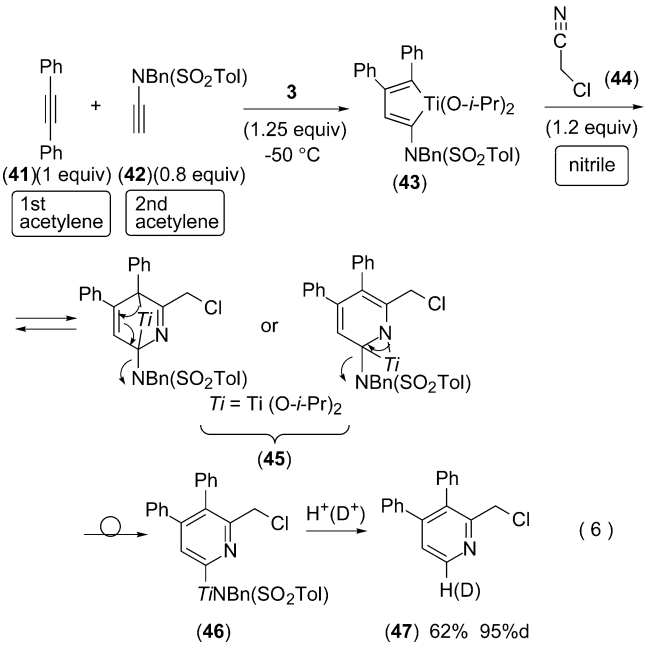
Scheme 5



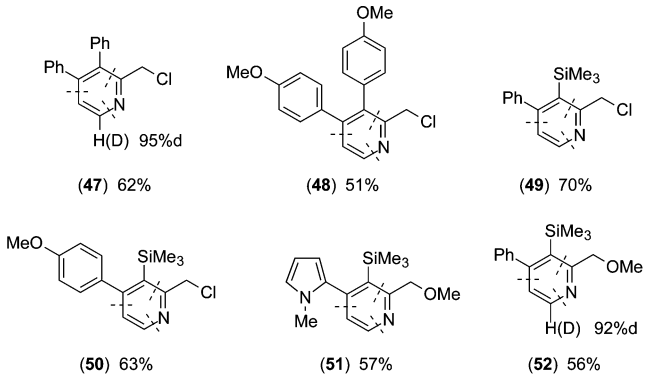
34), (ii) Grignard addition (**34** → **35**), and finally (iii) Swern oxidation afforded the intermediate **36**, which was cyclized under acidic conditions to give known benzocycloheptapyridine **30**[15b] in good yields for each step. More substituted derivatives **29** in Figure 1 may be analogously obtained by interception of the titanated pyridine **32** with an appropriate electrophile in place of the simple hydrolysis exemplified in Scheme 4.

Type-B Preparation of Pyridines from Two Acetylenes, One of Which Has a Leaving Group, and a Nitrile. The proposed mechanism of the cyclization of type A suggested that an acetylene having a leaving group (**37**, X = leaving group) could give a similar intermediate **39** like **11** or **12** in Scheme 3, even when the nitrile does not have a leaving group (Scheme 5). This intermediate **39** then collapses to give a metalated pyridine **40**, which is an alternative to the products of type-A transformation. The choice of the acetylene **37** is important, because reasonable candidates, halo- or sulfonyl acetylenes (an analogue of sulfonylnitrile **5**), proved not to be suitable for this purpose.[16] However, during the course of our study on the preparation and utility of (sulfonylamino)acetylenes,[17,18] we happened to find that these aminoacetylenes nicely fulfill the above requirement for the requisite acetylene **37**.

The coupling of internal acetylene **41** and (*p*-toluenesulfonylamino)acetylene **42**,[18] according to a published procedure,[17] generated the titanacyclopentadiene **43**, which was then allowed to react with nitrile **44** (eq 6). After aqueous workup, pyridine



(6)

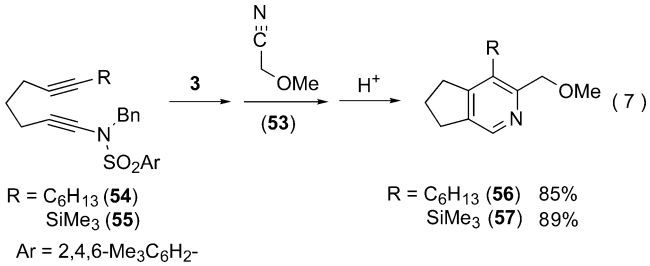


[a]Dotted lines show the position of newly formed carbon-carbon and carbon-nitrogen bonds.

Figure 2. Preparation of pyridines after hydrolysis or deuteriolysis of the reaction according of eq 6.

47 was selectively obtained in good yield. Alternatively, deuteriolysis gave **47**-*d*, confirming the presence of titanated pyridine **46** as an intermediate (type B, Scheme 1). The reaction path may be drawn as **43** → **45** → **46**, which was already proposed in Scheme 5. Apparently, the elimination of the sulfonamide group, which permits direct aromatization and thus makes the overall reaction irreversible, is a driving force of this reaction.

Other pyridines prepared by this method are summarized in Figure 2. Dianisylacetylene in place of diphenylacetylene (**41**) in eq 6 afforded pyridine **48**. Unsymmetrical acetylenes such as aryl(silyl)acetylenes underwent the regioselective coupling with aminoacetylene **42** to generate single titanacyclopentadienes, which reacted with nitrile **44** or α-methoxyacetonitrile (**53**) again in a highly regioselective manner to give single pyridines **49**−**52** in good yields. When α-methoxyacetonitrile (**53**) was used as a nitrile component instead of **44**, the formation of the corresponding metalated **52** before aqueous workup was again verified by deuteriolysis. In these reactions, α-heterosubstituted nitriles such as **44** and **53** are an acceptable choice for the nitrile, and they serve for the preparation of pyridines having an α-functionalized side chain; but simple octanonitrile or benzonitrile did not give the desired products.[19] Although the intermolecular coupling of acetylenes and nitriles shown in eq 6 and Figure 2 was so far successful only for the first acetylenes having at least one aryl group, an intramolecular version is not subject to such limitation. Thus, bicyclic pyridines **56** and **57** are available by the cyclization of aminodiynes **54** and **55** (eq 7), showing increasing synthetic flexibility.

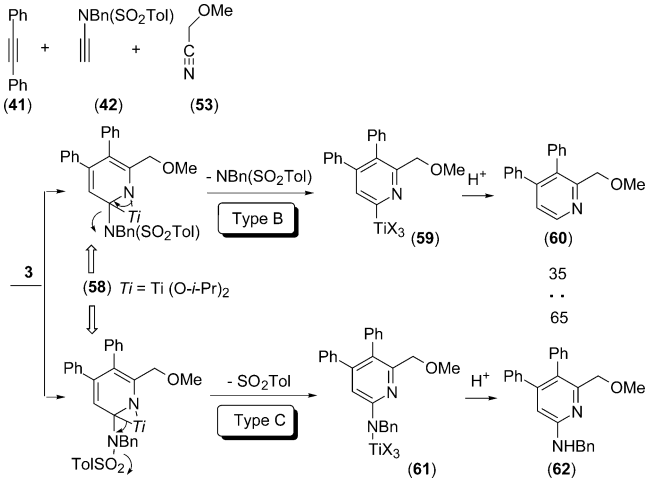


(7)

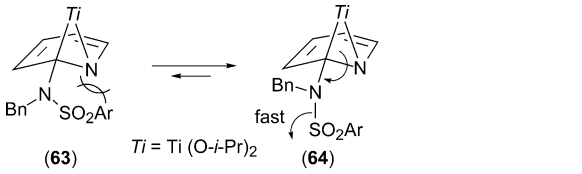
Type-C Preparation of Aminopyridines from Two Acetylenes, One of Which Has a Leaving Group, and a Nitrile.

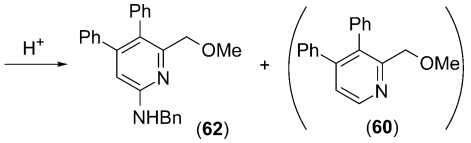
(16) Sulfonylacetylene and haloacetylene undergo the double addition to titanacyclopropene and the elimination of halide, respectively. See: Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **2001**, *123*, 7925−7926. Morlender-Vais, N.; Kaftanov, J.; Marek, I. *Synthesis* **2000**, 917−920.
(17) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett*. **2003**, *5*, 67−70.

Scheme 6. Preparation of Aminopyridines by Type-C Synthesis



Scheme 7. Choice of Leaving Group

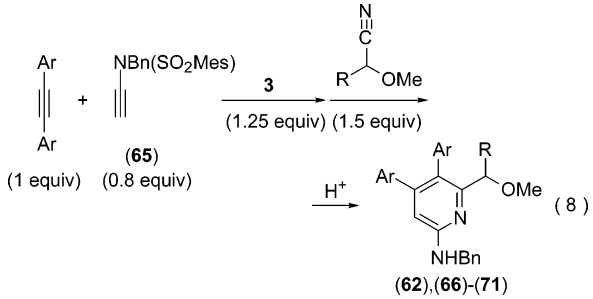




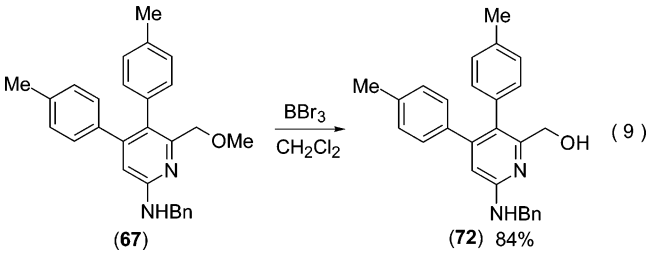
$ArSO_2$	Yield (%) of **62**	**62** : **60**
$TolSO_2$-	51%	65 : 35
$MesSO_2$-	62%	84 : 16

While we were investigating the type-B preparation of pyridines from diphenylacetylene (**41**) and α-methoxyacetonitrile (**53**) (rather than chloroacetonitrile **44** in eq 6), we found that an unknown product (**62**) became a major component accompanied by the expected pyridine **60** that was a minor component in the reaction this time (Scheme 6). Spectroscopic analysis showed the structure of the unknown compound to be aminopyridine **62** on the following basis that it lacks a *p*-toluenesulfonyl group but has a polar amino group as well as a pyridine ring. The manifold to the products **60** or **62** comes from the elimination of the sulfonylamino group from the common intermediate **58** to give **59** and finally **60** (type B) or that of the sulfonyl group from **58** to give **61** and **62** (type C). As aminopyridine is a useful functionalized pyridine derivative, we focused our attention on increasing its composition (Scheme 7). Facile elimination of the sulfonyl group should require a perpendicular relationship between the carbon−titanium and nitrogen−sulfonyl bonds as depicted in **64** of Scheme 7. Thus, the sterically demanding sulfonyl group may occupy the less hindered position **64** (rather than **63**), which fulfills the above assumption on the favorable orientation of the C−Ti and N−sulfonyl bonds. Actually, switching the amino-protecting group from *p*-toluenesulfonyl to bulky mesitylenesulfonyl ($MesSO_2$− = (2,4,6-$Me_3C_6H_2$)SO_2−) group increased the ratio (hence the yield) of the aminopyridine **62**.[20]

Equation 8 summarizes the type-C synthesis of aminopyridines utilizing [(mesitylenesulfonyl)amino]acetylene (**65**) as the second acetylene. A variety of diarylacetylenes and α-methoxynitriles afforded the aminopyridine derivatives **62** and **66**−**71**.[21] The methoxy group of product **67** could be readily demethylated with a routine reagent, BBr_3, to give the corresponding alcohol **72**, if necessary (eq 9).

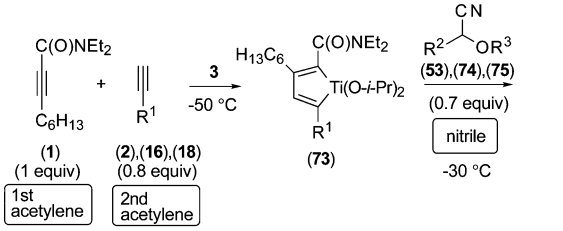


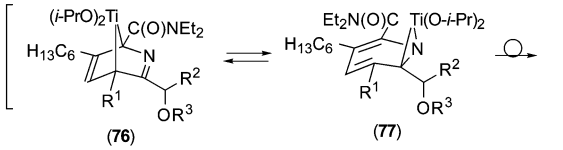
Diarylacetylene Ar	Nitrile R	Product	Yield (%)
Ph	H	**62**	62
Ph	Ph	**66**	50
p-MeC_6H_4	H	**67**	53
m-MeC_6H_4	H	**68**	57
p-(MeO)C_6H_4	H	**69**	67
p-(MeO)C_6H_4	Ph	**70**	53
p-ClC_6H_4	H	**71**	72

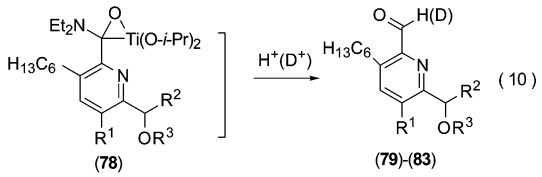


Type-D Preparation of Pyridinecarbaldehydes. In the preceding sections, the titanium-mediated coupling of acetylenes and a nitrile, one of which has a leaving group, furnished directly metalated pyridines. At first glance, the presence of a leaving group appears mandatory. However, we found that a certain functional group could work as a surrogate of the leaving group, which will be discussed in this section. Titanacyclopentadiene **73**, prepared from two different, unsymmetrical acetylenes **1** and **16**, was allowed to react with α-methoxyacetonitrile (**53**)

(18) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727−729.
(19) This suggests the importance of the presence of a coordinating moiety in the nitrile. See: ref 4 and the following. Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965−3968. Nonetheless, as α-oxynitriles and their derivatives are readily obtained by the cyanohydrin synthesis and its modifications, this reaction will find reasonable application. See: North, N., Ed. *Tetrahedron (Symposium-in-Print)* **2004**, *60*, 10385−10568.
(20) For examples of elimination of a leaving group on nitrogen by a neighboring carbanionic site, see: Schönberg, A.; Moubacher, R. *Chem. Rev.* **1952**, *50*, 261−277. Smith, R. F.; Walker, L. E. *J. Org. Chem.* **1962**, *27*, 4372−4375. Foley, H. G.; Dalton, D. R. *J. Chem. Soc., Chem. Commun.* **1973**, 628−629.
(21) Diarylheterocycles are frequently seen in derivatives of drugs. Toma, L.; Giovannoni, M. P.; Piaz, V. D.; Kwon, B.-M.; Kim, Y.-K.; Gelain, A.; Barlocco, D. *Heterocycles* **2000**, *53*, 2709−2718. Toma, L.; Nava, D.; Celentano, G.; Giovannoni, M. P.; Piaz, V. D.; Kwon, B.-M.; Kim, M.-K.; Kim, Y.-K.; Barlocco, D. *Heterocycles* **2000**, *53*, 2709−2718. Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479−2483. Stoit, A. R.; Lange, J. H. M.; Hartog, A. P.; Ronken, E.; Tipker, K.; Stuivenberg, H. H.; Dijksman, J. A. R.; Wals, H. C.; Kruse, C. G. *Chem. Pharm. Bull.* **2002**, *50*, 1109−1113. Kudo, N.; Furuta, S.; Taniguchi, M.; Endo, T.; Sato, K. *Chem. Pharm. Bull.* **1999**, *47*, 857−868.







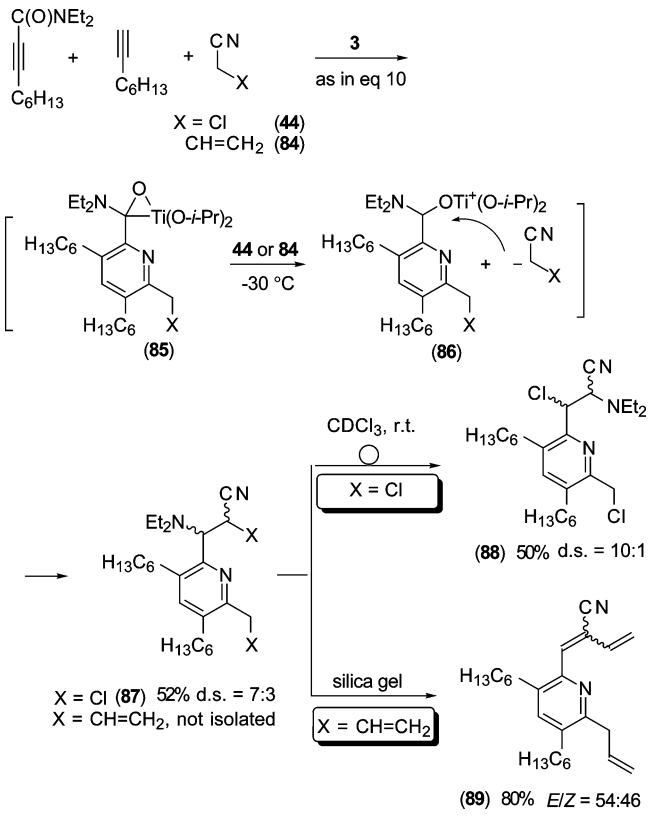
2nd acetylene		Nitrile			Product	
R^1		R^2	R^3			Yield (%)[a]
C_6H_{13}	**16**	H	Me	**53**	**79**	72-84 (83-99%d)[b]
Me_3Si	**18**	H	Me	**53**	**80**	65
Ph	**2**	H	Me	**53**	**81**	51
C_6H_{13}	**16**	H	Bn	**74**	**82**	90
C_6H_{13}	**16**	C_8H_{17}	Me	**75**	**83**	71

[a]Based on nitrile. [b]Depending on reaction scale. See the experimental section.

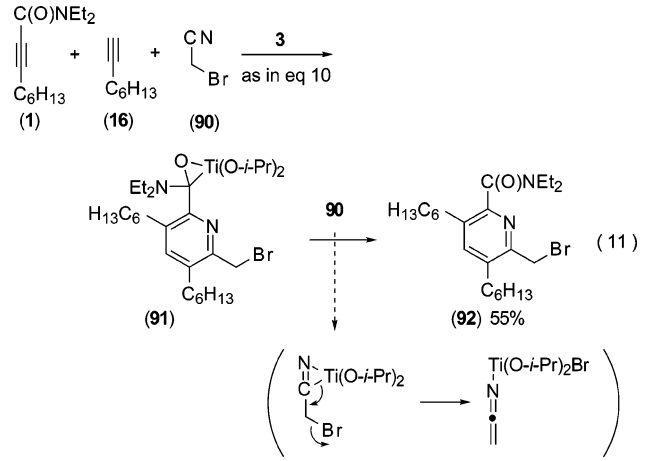
(eq 10). After aqueous workup, what we obtained was not a pyridineamide expected from the starting material **1** but was pyridinecarbaldehyde **79**, which was produced as a single isomer (eq 10, hence, type D in Scheme 1). To clarify the mechanism of this reaction, the above hydrolytic workup was replaced by deuteriolysis, which revealed that the aldehyde hydrogen of **79** was substituted by deuterium. On the basis of these observations, a plausible reaction course is shown in eq 10. The nitrile was regioselectively incorporated into the titanacycle **73** to generate the intermediate **76** or **77**, from which the titanium portion shifted to the amide group to result in the irreversible aromatization as well as the formation of η^2-carbonyl−titanium complex **78**.[22] Finally, hydrolysis (or deuteriolysis) of the η^2-carbonyl−titanium complex gave the (deuterated) aldehyde **79**.

Besides other products **80**−**83** obtained from a variety of acetylenes and nitriles as shown in eq 10, an intriguing utility of the metalated portion of **78** was demonstrated by its reaction with a pronucleophile. When the same reaction was started with excess α-chloroacetonitrile (**44**) or α-vinylacetonitrile (**84**) (Scheme 8), the reaction proceeded beyond the common intermediate **85** via the proton exchange reaction with the initially added nitrile (**85** → **86**). In the case of **44**, a new product **87** was finally produced and was isolated as a mixture of diastereoisomers. However, this product **87** spontaneously isomerized in $CDCl_3$ (by ^1H NMR monitoring) at room temperature overnight to yield another diastereomeric mixture of **88** in 50% yield based on the starting acetylenes. Similarly, when vinylacetonitrile (**84**) was used, two molecules of the nitrile were eventually incorporated to give pyridine **89** as a mixture of separable olefinic stereoisomers. It should be noted that the selective coupling of four

Scheme 8. Reaction of Various Nitriles



molecules was achieved in one pot in the overall reactions of Scheme 8.

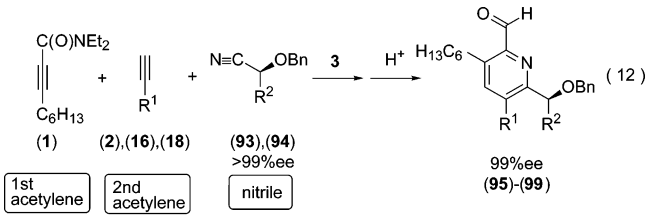


On the other hand, α-bromoacetonitrile (**90**) afforded a different pyridine **92** most likely via the titanium transfer reaction from the intermediate **91** to **90** to regenerate the amide group in **92** (eq 11)[23] rather than the proton transfer as shown in Scheme 8. That an appropriate choice of the substituted acetonitriles, **44**, **84**, or **90**, could lead to different types of

(22) For the generation of carbonyl group−group 4 metal complexes and their synthetic application, see: Erker, G.; Rosenfeldt, F. *J. Organomet. Chem.* **1982**, *224*, 29−42. Davis, J. M.; Whitby, R. J. *Tetrahedron Lett.* **1992**, *33*, 5655−5658. Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 5643−5649. Barluenga, J.; Sanz, R.; Fañanás, F. J. *Chem.−Eur. J.* **1997**, *3*, 1324−1336. Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 11295−11305.

(23) This may come from lower α acidity of **90** as compared to that of **44** or **84**. Moreover, the irreversible elimination of the most reactive bromo group (among **90**, **44**, and **84**) from titanated **90** should force the titanium transfer reaction from **91** to **90**.

substituted pyridines is an interesting aspect of this transformation.



2nd acetylene		Nitrile		Product	
R^1		R^2			Yield (%)
C_6H_{13}	**16**	Me	**93**	**95**	68
Me_3Si	**18**	Me	**93**	**96**	57
Ph	**2**	Me	**93**	**97**	51
C_6H_{13}	**16**	Ph	**94**	**98**	90
Ph	**2**	Ph	**94**	**99**	71

When the pyridine synthesis is started with optically active α-oxynitriles, optically active pyridinecarbaldehydes may be obtained. However, as the reaction conditions are apparently basic in the presence of titanium alkoxide, and the titanium in the intermediate **77** (eq 10) could undergo a *β*-hydrogen elimination/addition sequence to cause racemization, it is not necessarily guaranteed that the optical purity of the nitriles is retained throughout this reaction. Equation 12 shows the preparation of pyridinecarbaldehydes **95**−**99** from optically active lacto- or mandelonitriles **93** or **94**.[2e] To our satisfaction, the products always kept a high level of enantiopurity, indicating that the type-D reaction provides a straightforward method to prepare optically active pyridines in one pot.

Conclusion

Combination of two acetylenes, various nitriles, and the titanium alkoxide reagent produced a variety of titanated pyridines in four different ways. Some of these reactions executed a virtually completely regioselective coupling of two different, unsymmetrical acetylenes and a nitrile, which is a difficult task and is quite important from the synthetic point of view. In addition, as the starting materials and reagents required in this reaction are readily available, the present pyridine syntheses are practically preferable. The utility of the resultant titanated pyridines has been demonstrated through the reaction of representative electrophiles, which enables the coupling of four components in one pot. Further search for new versions of these reactions and synthetic utility of metalated pyridines is in progress.

Acknowledgment. This work was supported, in part, by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" (to F.S.) and Scientific Research on Priority Area "Creation of Biologically Functional Molecules" (to H.U.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and also by The Sumitomo Foundation (to H.U.). D.S. thanks the Japan Society for the Promotion of Science for a Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists. R.T. acknowledges a Grant of the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental section and complete refs 15c and 15d (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA050261E