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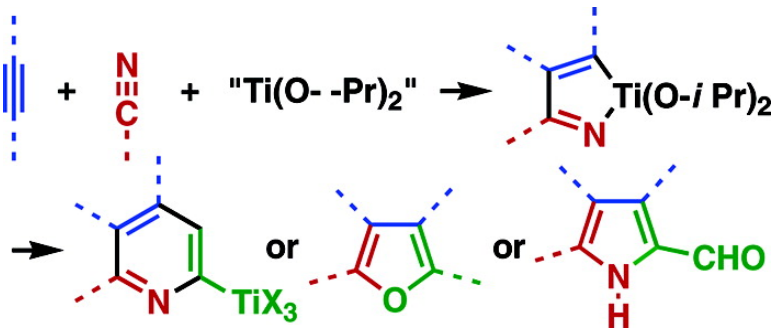

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Facile Preparation of Various Heteroaromatic Compounds via Azatitanacyclopentadiene Intermediates

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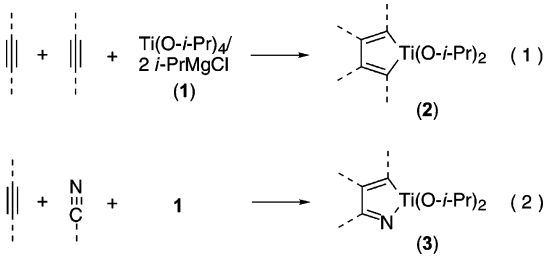
Abstract: Coupling of acetylene, nitrile, and a titanium reagent, Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl, generated new azatitanacyclopentadienes in a highly regioselective manner. Their subsequent reaction with sulfonylacetylene afforded pyridyltitanium compounds, which, upon reaction with electrophiles, gave substituted pyridines virtually as a single isomer. When optically active nitriles were used in this reaction, chiral pyridines were obtained without loss of the enantiopurity. Alternatively, the azatitanacyclopentadiene prepared from an unsymmetrical acetylene reacted with an aldehyde or another nitrile to give furans or pyrroles having four different substituents again in a regioselective manner.

Introduction

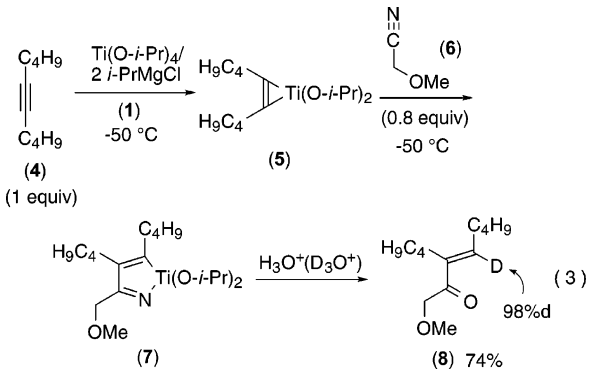
Titanacyclopentadienes **2** generated from acetylenes and a divalent titanium alkoxide reagent, Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl (**1**), have been utilized for various transformations (eq 1).[1,2] On the other hand, their nitrogen analogue, azatitanacyclopentadienes **3** possibly prepared by the same coupling reaction of acetylene and nitrile, has not yet been explored (eq 2), because the attempted generation of azatitanacyclopentadiene **3** from an alkanenitrile or benzonitrile is so far unsuccessful. However, we describe here that certain nitriles such as α-heterofunctionalized ones exceptionally undergo the titanium-mediated coupling with an acetylene to generate the desired azatitanacyclopentadiene **3** in good yield.[3]



(1)

(2)

Thus, 5-decyne (**4**) was first treated with a divalent titanium alkoxide reagent, Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl (**1**) at −50 °C, to give a known acetylene−titanium complex **5** (eq 3).[1,2] α-Methoxyacetonitrile (**6**) was added to complex **5** at the same temperature to form dialkoxyazatitanacyclopentadiene **7**, which was identified by hydrolysis or deuteriolysis to give α,β-unsaturated ketone **8** with high deuterium incorporation at the specified position in good yield.[4]



(3)

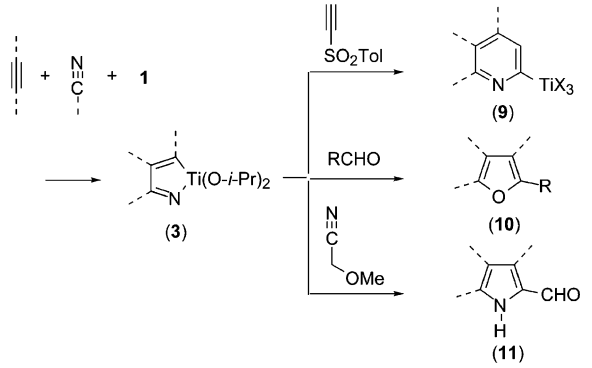
The azatitanacyclopentadienes **3**, as exemplified by **7** in eq 3, proved to be a useful intermediate for new synthesis of heterocyclic compounds such as metalated pyridines **9**, furans **10**, and pyrroles **11** through reaction with another unsaturated

[†] Department of Biomolecular Engineering.
[‡] Department of Biological Information.

(1) Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 319−354. Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759−784. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835−2886. Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511−1519.
(2) Eisch, J. J. *J. Organomet. Chem.* **2001**, *617*−*618*, 148−157. Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789−2834.
(3) For other azametallacyclopentadienes of group 4 metals, see: Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047−1058. Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, pp 1163−1184. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124−130. Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880−1889. Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802−6806.
(4) This suggests the importance of the presence of a coordinating moiety in the nitrile. See ref 8 and the following: Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965−3968. Nonetheless, since 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. Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4279−4280.

10.1021/ja0502730 CCC: $30.25

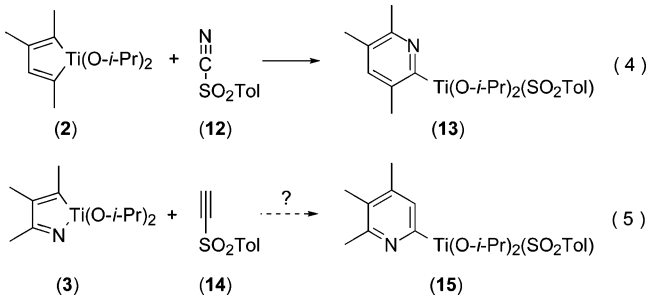
Scheme 1. Preparation of Heteroaromatic Compounds



compound, as summarized in Scheme 1. These transformations consist of an organized assembly of unsaturated compounds around the titanium reagent, allowing a one-pot, multicomponent coupling process, which will be described in order.

Results and Discussion

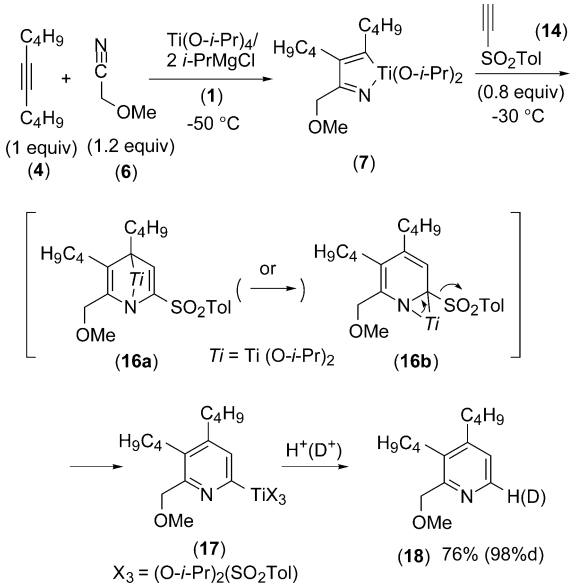
Preparation of Pyridines. Among a wide variety of preparative methods of pyridines,[5] cycloaddition of two acetylenes and a nitrile has attracted much attention.[6,7] Starting from titanacyclopentadienes **2**, we have recently reported a selective pyridine synthesis (i.e., **13**) by the coupling with *p*-toluenesulfonylnitrile (**12**, $TolSO_2$- = *p*-$MeC_6H_4SO_2$-) (eq 4).[8,9] If a similar reaction is started with azatitanacyclopentadienes **3** and these successfully undergo the uptake of a likely reaction partner, sulfonylacetylene **14**[10] in eq 5, metalated pyridines **15** with a different substitution pattern will be produced.



To azatitanacycle **7** generated from **4** and **6** as described in eq 3 was added sulfonylacetylene **14**,[11] and the reaction was continued at −30 °C (Scheme 2). Gratifyingly, the formation of a single pyridine **18** was observed after aqueous workup. The presence of the titanated pyridine **17** was separately confirmed by its deuteriolysis to give **18**-*d* with high deuterium incorporation. A proposed mechanism of this reaction is also depicted in Scheme 2. Sulfonylacetylene **14** was incorporated into the azatitanacycle **7** in a regioselective manner to give intermediates **16a**,**b**.[12] Elimination of the sulfonyl group from **16b** leads to the formation of the pyridyltitanium compound **17**.

Other results of the present pyridine synthesis are summarized in Table 1. Besides simple α-methoxyacetonitrile (**6**), a branched homologue **20** afforded the desired pyridine **21** (entry 2) and **25** (entry 5) in good yield. Silylacetylene **22** underwent the regioselective coupling with nitrile **6**, followed by the regioselective uptake of sulfonylacetylene **14**, to yield virtually single titanated pyridines, which, after hydrolysis or deuteriolysis, gave pyridine **23** or its deuterium-labeled compound **23**-*d* (entry 3). The synthetic utility of the pyridyltitanium species was further

Scheme 2. Preparation of Metalated Pyridine



(5) For reviews, see: (a) Katritzky, A. R., Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, U.K., 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.

(6) 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, Germany, 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, U.K., 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, U.K., 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.

(7) (a) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Chem. Commun.* **1973**, 280. (b) 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 8 and 9). For recent reports, which deal with the cyclotrimerization of the same (refs 7c−j), symmetrical (ref 7k), or tethered (refs 7l−r) substrates, see: (c) Bianchini, C.; Meli, A.; Peruzzini, M.; Vacca, A.; Vizza, F. *Organometallics* **1991**, *10*, 645−651. (d) Smith, D. P.; Strickler, J. R.; Gray, S. D.; Bruck, W. A.; Holmes, R. S.; Wigley, D. E. *Organometallics* **1992**, *11*, 1275−1288. (e) Viljoen J. S.; du Plessis, J. A. K. *J. Mol. Catal.* **1993**, *79*, 75−84. (f) Diversi, P.; Ermini, L.; Ingrosso, G.; Lucherini, A. *J. Organomet. Chem.* **1993**, *447*, 291−298. (g) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911−2924. (h) Jerome, K. S.; Parsons, E. J. *Organometallics* **1993**, *12*, 2991−2993. (i) Heller, B.; Oehme, G. *J. Chem. Soc., Chem. Commun.* **1995**, 179−180. (j) Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131−3133. (k) Takahashi, T.; Tsai, F.-Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994−4995. (l) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487−489. (m) Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett.* **1995**, 851−852. (n) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **1997**, *62*, 4189−4192. (o) Varela, J. A.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **1998**, *120*, 12147−12148. (p) Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **1999**, *1*, 2141−2143. (q) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2001**, 1102−1103. (r) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189−6190.

(8) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 3518−3519. This reaction has the following feature: (i) single pyridines were obtained, for the first time, from two different, unsymmetrical acetylenes and a nitrile, and (ii) titanated pyridines were produced rather than pyridines themselves.

(9) See also: 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.

(10) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925−7926.

(11) This is commercially available.

(12) The intermediates **16a**,**b** correspond to the [4 + 2]-type and insertion mechanisms, respectively. See: ref 10.

Table 1. Preparation of Pyridines

Entry	1st acetylene (**19**)	Nitrile	Electrophile	Product	Yield(%)
1	C_4H_9–≡–C_4H_9 (**4**)	NC(H)(OMe) (**6**)	$H^+(D^+)$	H_9C_4, OMe, H(D) (**18**)	76 (98%d)
2	"	$H_{17}C_8$, NC(H)(OMe) (**20**)	H^+	H_9C_4, $H_{17}C_8$, OMe (**21**)	63
3	$SiMe_3$–≡–C_6H_{13} (**22**)	NC(H)(OMe) (**6**)	$H^+(D^+)$	$H_{13}C_6$, $SiMe_3$, OMe, H(D) (**23**)	58 (94%d)
4	"	"	I_2	$H_{13}C_6$, $SiMe_3$, OMe, I (**24**)	50
5	"	$H_{17}C_8$, NC(H)(OMe) (**20**)	H^+	$H_{13}C_6$, $H_{17}C_8$, $SiMe_3$, OMe (**25**)	57
6	"	NC(H)(Cl) (**26**)	H^+	$H_{13}C_6$, $SiMe_3$, Cl (**27**)	53
7	$SiMe_3$–≡–Ph (**28**)	NC(H)(OMe) (**6**)	H^+	Ph, $SiMe_3$, OMe (**29**)	56

demonstrated by the preparation of iodopyridine **24** (entry 4).[13] It should be emphasized that this transformation achieved a completely organized assembly of two unsymmetrical acetylenes and a nitrile and, when including an electrophile, a four-component coupling process was executed in one pot. α-Chloroacetonitrile (**26**) similarly participated in the reaction to give (halomethyl)pyridine **27** (entry 6) in good yield after hydrolytic workup. Like 1-silyl-1-alkyne **22**, silyl(phenyl)acetylene **28** afforded the desired product **29** as well.

To prepare optically active pyridines, we carried out the reaction of Scheme 2 with chiral α-oxynitriles **30** and **31**[6e] as the starting material (eq 6). Since the reaction conditions are apparently basic in the presence of titanium alkoxide and the intermediate titanium species could undergo a β-hydrogen elimination/addition sequence to cause racemization at the benzylic position, the ee value of the products was individually determined. Figure 1 summarizes the products **32**−**39** obtained after routine hydrolysis, deuteriolysis, or iodinolysis. In all cases, as the enantiomeric excess of the products did not change from

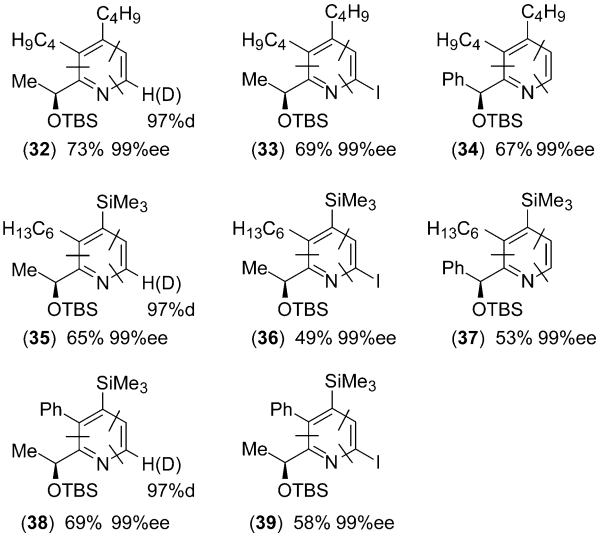
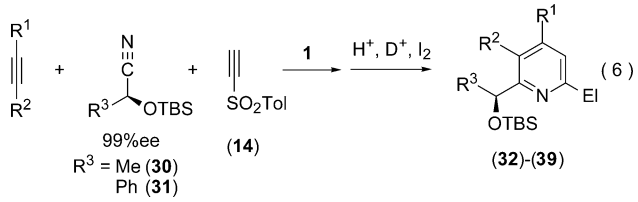


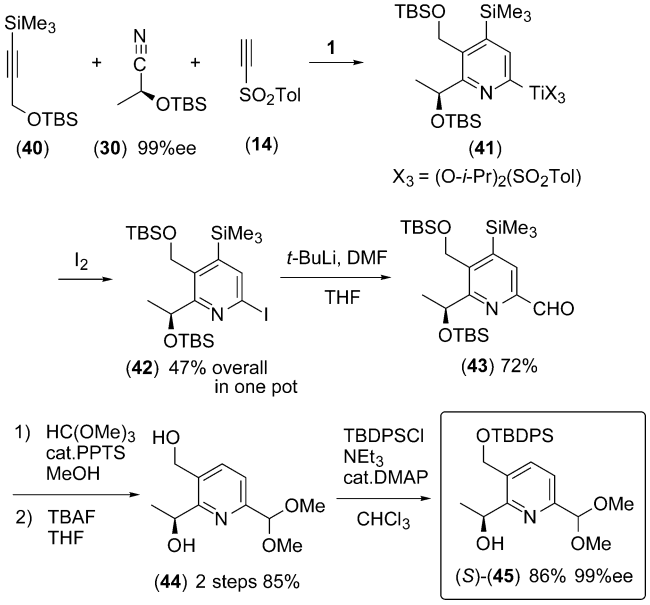
Figure 1. Preparation of optically active pyridines according to eq 6. Dotted lines show the position of newly formed carbon−carbon and carbon−nitrogen bonds.

that of the starting nitrile, a convenient preparative method of highly optically active pyridines was established.



Pyridine **45**, which is a potential intermediate for the synthesis of cyclothiazomycin (Scheme 3),[14] was efficiently prepared by

Scheme 3. Preparation of Pyridine **45**, a Key Compound to Cyclothiazomycin

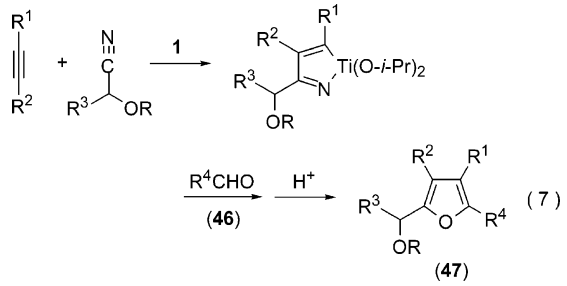


the above method. Acetylene **40**, chiral nitrile **30**, sulfonylacetylene **14**, and the titanium reagent **1** gave pyridyltitanium species **41**, which upon iodinolysis afforded single iodopyridine **42**. This compound was transformed to pyridinecarboxaldehyde **43** by the reaction with *t*-BuLi and dimethylformamide (DMF).

(13) 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, U.K., 1991; Vol. 1, pp 139−172. Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, U.K., 1994; pp 195−282. Urabe, H.; Hamada, T.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 2931−2932.

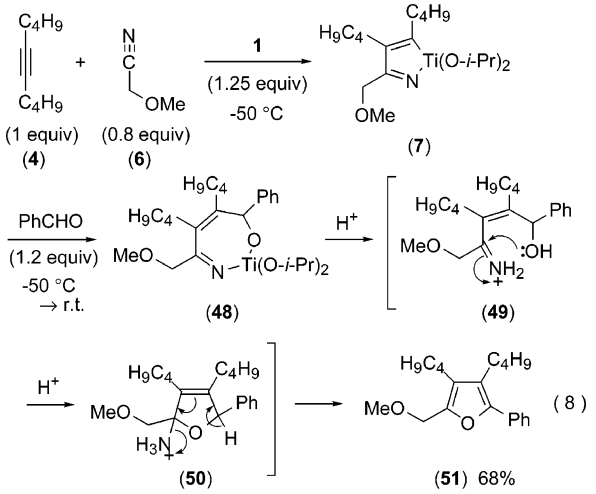
Then, acetalization and desilylation afforded pyridinediol **44**. Selective protection of its primary alcohol with *tert*-butyldiphenylsilyl chloride ((TBDPS)Cl) gave the desired compound **45** of 99% ee. Therefore, the key pyridine **45** was prepared in five steps, in 25% overall yield, and with high optical purity, improving its known synthetic route.[15]

Preparation of Furans. Since substituted furans are not only a constituent of biologically active compounds but also a useful intermediate in organic synthesis,[16] their preparation in short steps is quite desirable. During the course of our study, we found that an aldehyde **46** also reacts with the carbon−titanium bond of the azatitanacyclopentadiene to give directly polysubstituted furans **47** as formulated in eq 7.[17]



(7)

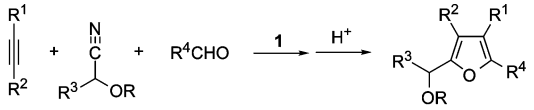
The experimental procedure is quite simple as illustrated in eq 8. To azatitanacyclopentadiene **7** generated from **4** and **6** was added benzaldehyde, and the reaction mixture was gradually warmed to room temperature to give adduct **48**. The reaction mixture was quenched with 1 N HCl, which effected the spontaneous cyclization and aromatization of **48** most likely via **49** to **50**, eventually giving fully substituted furan **51**.



(8)

Other results are summarized in Table 2. An aliphatic aldehyde, nonanal, in place of the benzaldehyde in entry 1 furnished furan **52** in good yield (entry 2). Notably, an unsymmetrical acetylene such as 1-(trimethylsilyl)-1-octyne (**22**), nitrile **6**, and an aldehyde afforded furans **54**−**56** having four different substituents with nearly complete regioselectivity (entries 4−6). Diphenylacetylene (**57**) and benzaldehyde provided polyaromatic compound **58** in good yield (entry 7). Among many known preparations of polysubstituted furans, this multicomponent coupling process should provide an extremely concise synthetic method.

Table 2. Preparation of Fully Substituted Furans



Entry	Acetylene	Nitrile	Aldehyde	Product	Yield(%)
1	C_4H_9, C_4H_9 (**4**)	OMe (**6**)	PhCHO	H_9C_4, C_4H_9, MeO, Ph (**51**)	68
2	"	"	$C_8H_{17}CHO$	H_9C_4, C_4H_9, MeO, C_8H_{17} (**52**)	60
3	"	$H_{17}C_8$, OMe (**20**)	PhCHO	H_9C_4, C_4H_9, MeO, Ph, $H_{17}C_8$ (**53**)	57
4	$SiMe_3$, C_6H_{13} (**22**)	OMe (**6**)	PhCHO	$H_{13}C_6$, $SiMe_3$, MeO, Ph (**54**)	57
5	"	"	$C_8H_{17}CHO$	$H_{13}C_6$, $SiMe_3$, MeO, C_8H_{17} (**55**)	55
6	"	$H_{17}C_8$, C_8H_{17} (**20**)	PhCHO	$H_{13}C_6$, $SiMe_3$, MeO, Ph, $H_{17}C_8$ (**56**)	54
7	Ph, Ph (**57**)	OMe (**6**)	PhCHO	Ph, Ph, MeO, Ph (**58**)	66

Preparation of Pyrrolecarboxaldehydes. Functionalized pyrroles are ubiquitous constituents in natural and artificial organic compounds and are versatile starting materials for their synthesis as well.[18] Among such pyrroles, pyrrolecarboxaldehydes are one of the most representative members. However, concise preparation of pyrrolecarboxaldehydes themselves,

(14) Okabe, A.; Ito, A.; Okamura, K.; Shin, C. *Chem. Lett.* **2001**, 380−381. Shin, C.; Okabe, A.; Ito, A.; Ito, A.; Yonezawa, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1583−1596. Endoh, N.; Yonezawa, Y.; Shin, C. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 643−644.

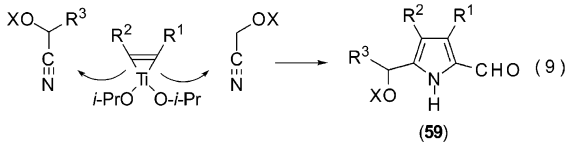
(15) Pyridine **45** was previously prepared in 10 steps, in 8% overall yield, and as 96% ee from 1,1-dimethoxy-2-propanone. See: ref 14.

(16) For reviews, see: Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955−2020. Katritzky, A. R., Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, U.K., 1984; Vol. 4. References 5b,e.

(17) Intermolecular double addition of acetylene−group 4 metal complexes to electrophilic carbon−heteroatom multiple bonds such as aldehydes, ketones, and imines is quite rare and is so far limited to a reactive acetylene complex such as that derived from enyne or an active electrophile represented by carbon dioxide: Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138−7139. Gao, Y.; Shirai, M.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 6849−6852. Six, Y. *Eur. J. Org. Chem.* **2003**, 1157−1171. To the contrary, the selective monoaddition of acetylene−group 4 metal complexes to these compounds is well-documented in the following reviews. See: refs 1−3.

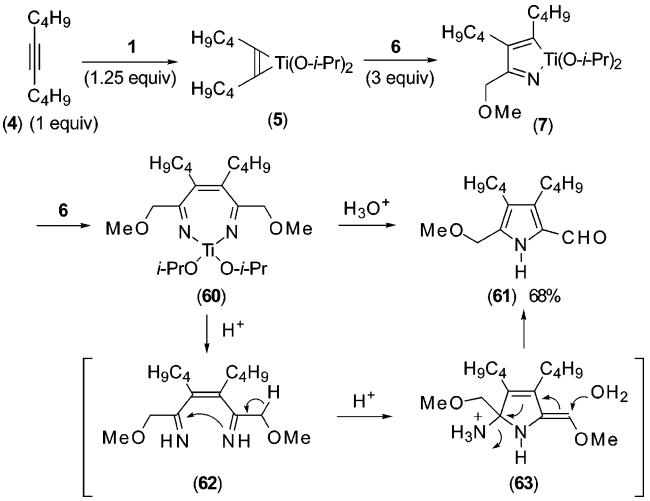
(18) Ferreira, V. F.; de Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proc. Int.* **2001**, *33*, 411−454. Katritzky, A. R., Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, U.K., 1984; Vol. 4. References 5b,e.

especially that of polysubstituted ones in a regioselective manner, is quite limited, because they are usually derived from the parent pyrroles in a stepwise manner.[18,19] In this section, we describe a novel and straightforward synthesis of pyrrolecarboxaldehydes **59** via azatitanacyclopentadienes as formulated in eq 9.



When excess nitrile **6** was allowed to react with the acetylene−titanium complex **5**, the 1:1 adduct **8** (see eq 3) became a minor component, and, instead, a new product, pyrrolecarboxaldehyde **61**, was isolated after acidic workup of the reaction mixture (Scheme 4).[20] This compound was most

Scheme 4. Preparation of Pyrrolecarboxaldehyde from Acetylene and Nitrile



likely produced via the double addition of the nitrile to the acetylene complex **5**,[17,21] and the resultant diazatitanacycloheptatriene **60** was hydrolyzed to diimine **62**, which underwent ring closure via the enamine intermediate to give five-membered nitrogen cycle **63**. Elimination of the ammonium group from **63** with concomitant hydration of the terminal vinyl ether moiety gave the observed pyrrolecarboxaldehyde **61** as the final product.

The same reaction starting with an unsymmetrical acetylene **64** shown in Scheme 5 illustrates the viable regiochemical control in the present transformation. Upon reaction with nitrile **6** (3 equiv), acetylene complex **65** afforded the regioisomeric pyrrolecarboxaldehydes **67** in equal amounts. Thus, the ring closure from **66a** to **67** (through both paths *a* and *b*) could not be controlled by the substituents (Ph and C_4H_9). On the other

Scheme 5. Regiochemical Aspects of the Pyrrole Formation

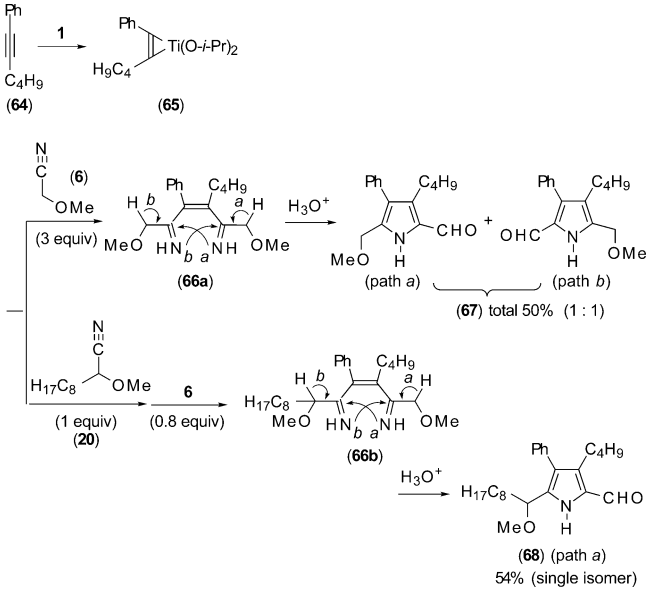
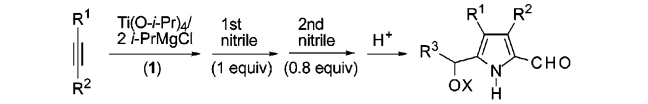
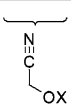
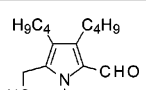
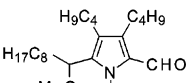
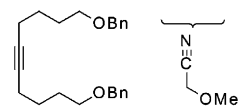
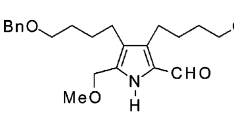
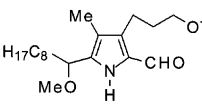
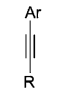
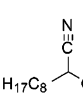
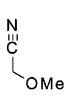
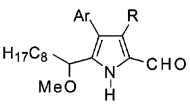
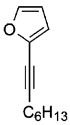
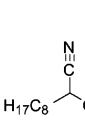
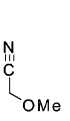
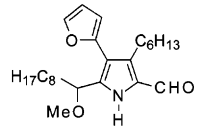
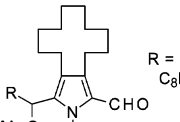


Table 3. One-Pot Preparation of Various Pyrrolecarboxaldehydes



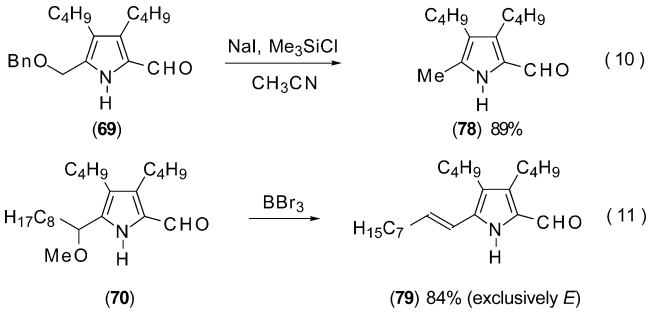
Entry	Acetylene	1st nitrile[a]	2nd nitrile[a]	Pyrrole[b]	Yield (%)[c] [Ratio]
1 2					X = Me (**61**) 68 Bn (**69**) 52
3					(**70**) 50
4					(**71**) 52
5					(**72**) 54 [80:20]
					
6 7 8				R = C_4H_9- Ar = Ph C_6H_{13}- *p*-ClC_6H_4- C_4H_9- *p*-(MeO)C_6H_4-	(**68**) 54 (**73**) 50 (**74**) 51
9					(**75**) 52
10 11					R = H (**76**) 66 C_8H_{17} (**77**) 50

[a] When the first and second nitriles are the same, 3 equiv of the nitrile was added in one portion. [b] Where applicable and unless otherwise stated, the depicted product was obtained as a single regioisomer. When the ratio is specified, the major regiosisomer is shown. [c] Isolated yield.

(19) Gschwend, H. W.; Rodriguez, H. R. In *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1979; Vol. 26, pp 1−360.
(20) For other syntheses of pyrroles by the use of metalacycles of group 4 metals, see: Buchwald, S. L.; Wannamaker, M. W.; Watson, B. T. *J. Am. Chem. Soc.* **1989**, *111*, 776−777. Gao, Y.; Shirai, M.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 7787−7790. Nakamoto, M.; Tilley, T. D. *Organometallics* **2001**, *20*, 5515−5517.
(21) To our best knowledge, the double addition of acetylene−group 4 metal complexes to nitriles has not been reported (see ref 3). A relevant double addition of a titanacycle to nitriles was only reported for titanacyclobutenes, yielding pyridines after aqueous workup: Doxsee, K. M.; Mouser, J. K. M. *Organometallics* **1990**, *9*, 3012−3014.

hand, the successive coupling of **65** with two different nitriles **20** (1 equiv) and **6** (0.8 equiv) proceeded in a regioselective manner, leading to the selective generation of a single pyrrolecarboxaldehyde **68** resulting solely from the cyclization of path *a* in **66b**. Formation of the sterically less encumbered trisubstituted enamine or the higher acidity of the methylene proton in **66b** may account for the preference for path *a* over path *b*.[22] It should be emphasized that the latter reaction allowed the selective preparation of pyrroles having four different substituents. The ready availability of the requisite α-oxynitriles by the cyanohydrin and related reactions[4] and the one-pot procedure as illustrated above should reinforce the synthetic advantage of this method.

Additional results summarized in Table 3 show the generality of the present synthesis of pyrrolecarboxaldehydes. α-Benzyloxynitrile could be used as well in place of methoxynitriles to give **69** (entry 2). An unsymmetrical dialkylacetylene showed reasonably good regioselectivity, giving **72** as the major isomer (entry 5). Aromatic acetylenes having a functional group on the phenyl group in entries 7 and 8 afforded virtually single products **73** and **74**, as discussed in Scheme 5. Analogously, pyrrole **75** having an additional hetereoaromatic group can be prepared by the present method (entry 9). Macrocyclic pyrroles **76** and **77** were conveniently obtained in good yields from the corresponding cycloalkyne[23] (entries 10 and 11). Since an α-alkoxy group in the products could be deprotected,[24] deoxygenated (to **78**, eq 10), or eliminated to give olefin **79** (eq 11), the oxygen functional groups at the α and α′ positions of the pyrroles[25] will facilitate further synthetic elaboration.



Conclusion

A concise synthesis of polysubstituted pyridines, furans, and pyrrolecarboxaldehydes has been achieved by the titanium-mediated assembly of acetylene, α-oxynitrile, and an additional unsaturated compound. The reaction was highly regioselective to afford these heteroaromatic compounds virtually as a single isomer. In addition, as the starting materials and reagents required in this reaction are readily available, the present syntheses are preferable from a practical point of view. Further investigation on the preparation of new heterocyclic compounds is now in progress.

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Supporting Information Available: Experimental Section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0502730

(22) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 570−581.
(23) Brummond, K. M.; Gesenberg, K. D.; Kent, J. L.; Kerekes, A. D. *Tetrahedron Lett*. **1998**, *39*, 8613−8616.
(24) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 14−86.
(25) α,α′-Dioxygenated pyrroles themselves recently attract interest in medicinal chemistry. Schweitzer, B. A.; Loida, P. J.; CaJacob, C. A.; Chott, R. C.; Collantes, E. M.; Hegde, S. G.; Mosier, P. D.; Profeta, S. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 1743−1746.