Highly Regioselective Synthesis of 3,4-Disubstituted 1*H*-Pyrrole[†,1]

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A highly regioselective method for the synthesis of 3,4-disubstituted 1*H*-pyrroles has been developed employing the ipso-directing property of a trimethylsilyl group. As a key starting material in this study, the known 3,4-bis(trimethylsilyl)-1*H*-pyrrole (**3**), was protected with carefully chosen groups, namely *tert*-butoxycarbonyl, *N*,*N*-dimethylaminosulfonyl, *p*-toluenesulfonyl, and triisopropylsilyl. A highly regioselective monoiodination of these 1-protected pyrroles was achieved by reaction with iodine−silver trifluoroacetate at low temperatures. Subsequent palladium-catalyzed cross-coupling reactions afforded 1-protected-4-substituted 3-trimethylsilyl-1*H*-pyrroles, which again underwent further room-temperature ipso-iodination and palladium-catalyzed cross-coupling reactions to provide symmetrical and unsymmetrical 1-protected-3,4-disubstituted 1*H*-pyrroles. Deprotection of 1-(*tert*-butoxycarbonyl) and 1-(*N*,*N*-dimethylaminosulfonyl) groups was found to be nontrivial. The 1-(*p*-toluenesulfonyl) protecting group was eventually proved to be superior to other protection groups, because it was readily removed after stepwise ipso monoiodinations and palladium-catalyzed cross-coupling reactions.

Introduction

The syntheses of pyrroles are by all means an attractive area in heterocyclic chemistry,[2] due primarily to the fact that many pyrroles are subunits of natural products[3] and some are the building blocks for porphyrin synthesis.[4] In particular, 3,4-disubstituted 1*H*-pyrroles have generated considerable interest owing to their remarkable diversity of biological activity.[5] A number of these compounds have been shown to possess antidiabetic,[6a] fungicidal,[6b] or antibacterial[6c] properties. However, it is also noteworthy that the 3,4-disubstituted pyrrole system is probably the most difficult to be prepared since most electrophilic aromatic substitution reactions as well as lithiation reactions of pyrrole rings occur predominantly at the α-position.[7] Selective substitutions at one or more of the *β*-positions have been generally believed to be a challenging goal in many synthetic programs. In the literature, several approaches to 3,4-disubstituted pyrroles have been recorded,[8] but it appears that they are less versatile for the realization of more elaborate substitution patterns.

The use of silicon in organic synthesis has attracted a great deal of interest because of the unusual properties that silicon conveys to organic molecules.[9] The ability of silicon to stabilize a carbocation at the *β*-position, known

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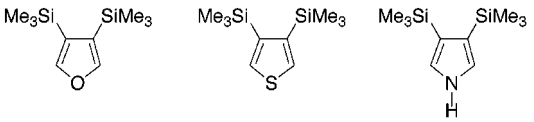
as the β-effect,[10] has been widely used in most reactions that involve silicon−carbon bond cleavage, leading to the ipso displacement of a silicon-contained group such as a trimethylsilyl group by other substituents. These substitution−desilylation reactions were first used for the regiospecific synthesis of several interesting disubstituted benzene derivatives.[11] Recently, the successful conversions of 3,4-bis(trimethylsilyl)furan (**1**)[12] to 3,4-disubstituted furans and 3,4-bis(trimethylsilyl)thiophene (**2**)[13] to 3,4-disubstituted thiophenes have been achieved in our laboratory involving the concomitant duties of a silyl group both as a protecting group and as an ipso director. The similarities of furan and thiophene to pyrrole prompted us to investigate the synthesis of 3,4-bis(trimethylsilyl)-1*H*-pyrrole (**3**), to which different substituents may be introduced into the β-carbons of the pyrrole ring through stepwise halodesilylation and subsequent palladium-catalyzed cross-coupling reactions. It is anticipated that **3** might offer a general entry toward the synthesis of symmetrical and unsymmetrical 3,4-disubstituted-1*H*-pyrroles.



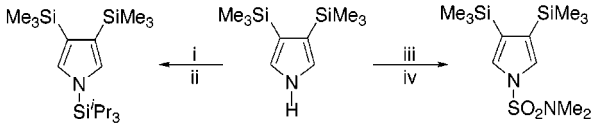
1 **2** **3**

The successful preparation[1,14] of **3** and its protection[14] with *tert*-butoxycarbonyl and *p*-toluenesulfonyl groups were reported recently. The iodination of 1-protected 3,4-bis(trimethylsilyl)-1*H*-pyrroles was also disclosed.[1] Herein, we would like to present details of the synthesis of some structurally elaborate 1-substituted and 1-unsubstituted 3,4-disubstituted 1*H*-pyrroles.

Results and Discussion

1. Protection of 3,4-Bis(trimethylsilyl)-1*H*-pyrrole (3). Our desired molecule **3** was obtained from 1-trimethylsilyl-2-aziridinecarbonitrile[15] through a 1,3-dipolar cycloaddition[16] with bis(trimethylsilyl)acetylene.[1,14] Due to the π-excessive pyrrole's acid sensitivity, high reactivity, and inferior stability,[17] 1-protection is therefore required before further reactions. Moreover, by varying the substituents on the nitrogen, a broad reactivity spectrum will become possible. In our special case, the choice of protecting group was restricted to those that do not require acidic conditions for group introduction as well as group removal because **3** undergoes even a facile ipso protodesilylation in dilute aqueous HCl. In the literature, two kinds of pyrrole protections are known, i.e., electron-donating protecting groups and electron-withdrawing groups. The latter is much superior to the former, due to its ability to reduce the electron density of the π-excessive pyrrole system, thereby increasing the stability of the pyrrole ring. In our previous study,[1,14] *tert*-butoxycarbonyl and *p*-toluenesulfonyl groups were chosen as protecting groups for this purpose. The *tert*-butoxycarbonyl group (Boc) can easily be introduced and removed.[18] The toluenesulfonyl group (Ts) can also be easily introduced and is stable under a wide variety of reaction conditions.[19] In addition to *tert*-butoxycarbonyl and *p*-toluenesulfonyl, triisopropylsilyl (TIPS) and *N*,*N*-dimethylaminosulfonyl groups (DMAS) were also selected for 1-protection. The use of triisopropylsilyl group for pyrrole protection has been recorded,[1,20] and its compatibility with mild protection and deprotection conditions encountered in substituted pyrrole synthesis has also been demonstrated.[20] Thus, protection of the nitrogen atom of **3** was accomplished in 95% yield by the use of ^{i}Pr$_3$SiCl and *n*-BuLi as base at −78 °C, as described by Bray and co-workers,[20] to afford 1-triisopropylsilyl-3,4-bis(trimethylsilyl)-1*H*-pyrrole (**4**) (Scheme 1). Pyrrole **4** formed a colorless liquid at room temperature and was extremely acid sensitive (vide infra). The two singlets at δ 0.22 and 6.88 in its ^{1}H NMR spectrum indicated its high level of symmetry, and absorptions at δ 1.09 and 1.43 were due to the isopropyl protons. Unlike the other three aforementioned protecting groups, to our best knowledge, *N*,*N*-dimethylaminosulfonyl[21] has never been employed for pyrrole protection. The formation of **5** took place smoothly by slow addition of a DMF solution of **3** to a cooled solution of NaH in the same solvent and was followed by the addition of $ClSO_2NMe_2$ to furnish **5** in a good yield (Scheme 1). The ^{1}H NMR spectrum of **5** showed a singlet at δ 2.81 for the six methyl protons of the *N*,*N*-dimethylaminosulfonyl group.

Scheme 1[a]



4 **3** **5**

[a] Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 20 min; (ii) *i*-Pr$_3$SiCl, −78 °C, 30 min, −78 °C to rt, 15 min, 95%; (iii) NaH, DMF, 0 °C, 2 h; (iv) $ClSO_2NMe_2$, 0 °C to rt, 2 h, 97%.

The removal of the *tert*-butoxycarbonyl group from the known 1-(*tert*-butoxycarbonyl)-3,4-bis(trimethylsilyl)-1*H*-pyrrole (**6**)[14] to form **3** was achieved efficiently by the use of NaOMe in MeOH. Under these conditions, the two trimethylsilyl groups of **6** remained intact. Likewise, the *p*-toluenesulfonyl group can also be removed readily from

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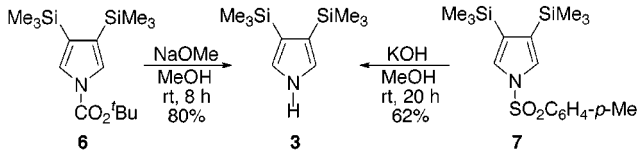
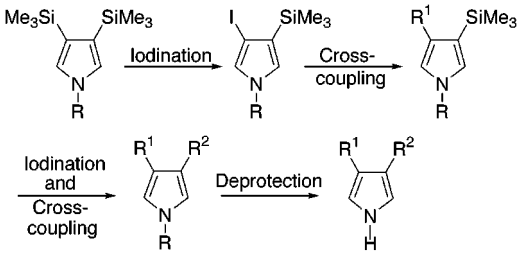
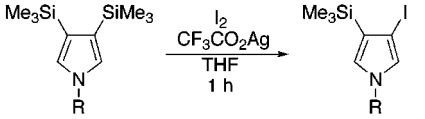
Scheme 2



Scheme 3



Scheme 4



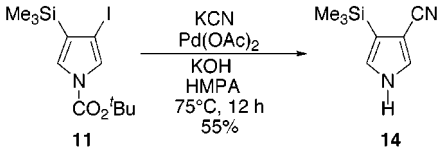
4 R = Si^{i}Pr$_3$	-78°C	**9**	85%
5 R = SO_2NMe_2	-35°C	**10**	83%
6 R = $CO_2{}^t$Bu	-55°C	**11**	92%
7 R = $SO_2C_6H_4$-*p*-Me	-45°C	**12**	84%
8 R = ^{t}Bu	-78°C	**13**	66%

1-(*p*-toluenesulfonyl)-3,4-bis(trimethylsilyl)-1*H*-pyrrole (**7**)[14] by reaction with KOH in MeOH, affording the parent **3** in good yield (Scheme 2).

2. Iodination of 1-Protected 3,4-Bis(trimethylsilyl)-1H-pyrroles. With 1-protected 3,4-bis(trimethylsilyl)-1*H*-pyrroles **4**, **5**, **6**, and **7** in hand, a practical avenue toward 3,4-disubstituted 1*H*-pyrrole was therefore sought, making use of repeated and stepwise ipso iodinations and palladium-catalyzed cross-coupling reactions. Thus, as depicted in Scheme 3, our initial attempt was to replace one of the two trimethylsilyl groups with an iodo group by employing the β-effect[10] of the trimethylsilyl group. Subsequently, 1-protected 3-trimethylsilyl-4-iodo-1*H*-pyrroles were converted through palladium-catalyzed cross-coupling reactions to lead to 1-protected-4-substituted 3-trimethylsilyl-1*H*-pyrroles. The remaining trimethylsilyl group was expectedly replaced again by other substituents through repeated iodination and cross-coupling reactions to form 3,4-disubstituted-1*H*-pyrroles after deprotection (Scheme 3).

The C−Si bond can be easily cleaved by I_2 due to the σ-donating character of a trimethylsilyl group,[22] as well as its β-effect.[10] A direct iodination using iodine and silver trifluoroacetate in THF at low temperature (usually −78 °C) was perfomed since furan **1**[12] and thiophene **2**[13] were both iodinated under similar conditions. In this way, efficient conversions of 1-protected 3,4-bis(trimethylsilyl)-1*H*-pyrroles **4**, **5**, **6**, **7**, and **8** (prepared from a similar route as that for **3**) into regiospecific monoiodides **9**−**13** were achieved in acceptable yields within 1 h at low temperature using I_2/CF_3CO_2Ag as shown in Scheme 4. It is worthy to note that in all cases only one trimethylsilyl group underwent iododesilylation at low temperatures (−35 to −78 °C) when 1 equiv of I_2 was used. The displacement of both trimethylsilyl groups was possible only when the reactions were carried out at room temperature and in the presence of an excess of I_2. Consequently, the iododesilylation of the remaining trimethylsilyl group was always performed at room temperature (vide infra).

Scheme 5



It is obvious that the reactivity was affected by the 1-substituents. Pyrroles **4** and **8**, bearing σ-donors at their nitrogen atoms, were clearly more reactive than the other three less electron-rich pyrroles. From the observed reaction temperatures, it is likely that the relative order of reactivity for these five 1-protecting groups is *t*-Bu ∼ *i*-Pr_3Si > *t*-BuOCO > *p*-$MeC_6H_4SO_2$ > SO_2NMe_2. This trend is in full agreement with the electronic effect exerted by these 1-substituents. The structures of **9**−**13** were unequivocally established by their ^{1}H NMR spectral data.

3. Preparation of 3,4-Disubstituted 1*H*-Pyrroles. The iodo groups of **9**−**13** served as pivotal handles from which many functional group conversions can be realized. For example, pyrrole **11** was readily converted to its cyano derivative **14** by reaction with KCN and $Pd(OAc)_2$ under basic conditions (Scheme 5).[23] The *tert*-butoxycarbonyl group was, however, also removed concomitantly.

Despite the fact that palladium-catalyzed cross-coupling reactions have been widely used in organic synthesis, the application of these coupling reactions on pyrroles has not been studied in a systematic manner. Herein our attention will be focused on the palladium-catalyzed cross-coupling reactions.

(a) 3,4-Disubstituted 1*H*-Pyrroles from 1-(*tert*-Butoxycarbonyl)-3-trimethylsilyl-4-iodo-1*H*-pyrrole (11). The palladium-catalyzed cross-coupling strategy between iodoarenes and terminal alkynes,[24] alkenes,[25] and areneboronic acid[26] offered important routes for the functionalization of pyrroles at their β-carbons. 1-(*tert*-Butoxycarbonyl)-protected pyrrole **11** was first used for this purpose. It was found that the palladium-catalyzed Sonogashira reaction[24] proceeded smoothly under mild conditions. Four alkynyl-substituted pyrrole compounds **15**−**18** were prepared in good yields via treatment of the iodide **11** with different terminal alkynes in the presence of a catalytic amount of palladium(0), a secondary amine

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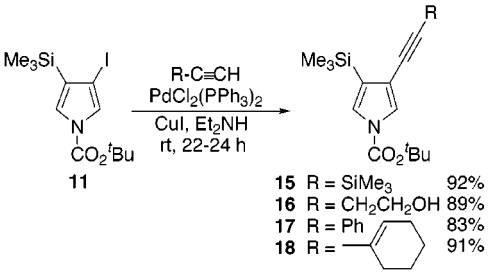
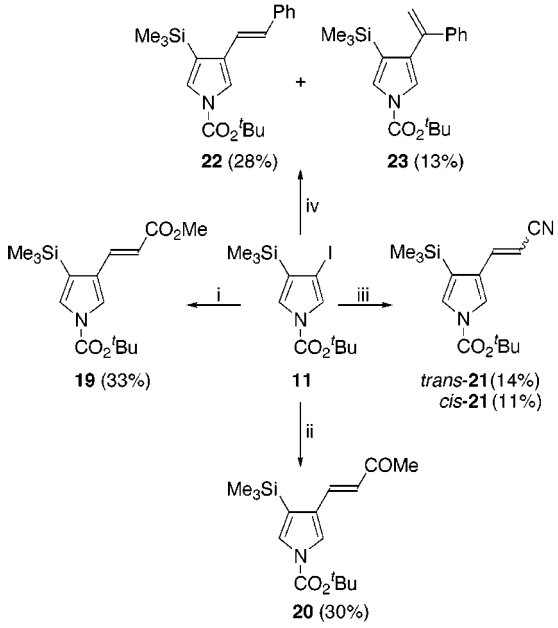
Scheme 6



as base, and CuI as cocatalyst (Scheme 6).[27] The active Pd(0) catalyst was generated in situ from $Pd(PPh_3)_2Cl_2$ and CuI in diethylamine. It was recorded in the literature that CuI facilitated alkynylation of the Pd(II) intermediate.[28] The ^1H and ^{13}C NMR spectral assignments of compounds **15**, **16**, **17**, and **18** were straightforward, and all significant absorptions were easily assigned.

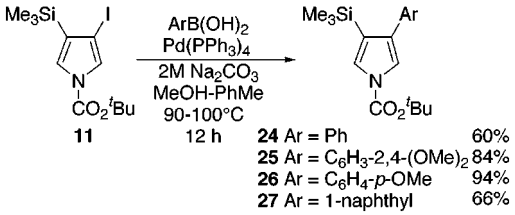
The Heck reaction[25] has become an invaluable method for introducing ethenyl substituents including acrylate ester moieties on heterocycles. 3-Trimethylsilyl-4-iodofuran[12] and 3-trimethylsilyl-4-iodothiophene[13] readily reacted with alkyl acrylates, acrylonitrile, styrene, and methyl vinyl ketone. However, such alkenylation of pyrrole **11** was found to be very difficult under the regular Heck reaction conditions, i.e., $Pd(OAc)_2$ and PPh_3 in triethylamine under reflux,[29] in that pyrrole **11** failed to form the acrylyl derivative from an excess of methyl acrylate and $Pd(OAc)_2-PPh_3$ at 100−120 °C. Instead, it gave only recovered pyrrole **11** and an intractable brown viscous oil. Likewise, **11** did not give the alkenylpyrrole derivatives through similar reactions with styrene or methyl vinyl ketone. Eventually, it was discovered that this drawback could be remedied by the use of $PdCl_2(PPh_3)_2$. Thus, alkenylation of **11** with methyl acrylate was achieved using the following procedure: an excess of terminal alkene (14 equivalents) was added to a refluxing mixture of **11** in Et_3N and DMF containing a catalytic amount of $PdCl_2(PPh_3)_2$. By using this method, several alkenylpyrroles **19**−**23** were obtained. The stereochemistry of the products was different due to different substrates.[30] For example, with methyl acrylate and methyl vinyl ketone, **11** gave exclusively the trans-disubstituted alkenes **19** and **20**, while reaction with acrylonitrile gave a mixture of *trans*-**21** as well as the *cis*-**21**. A similar situation was also found for styrene; i.e., the *gem*-isomer **23** was obtained in addition to the trans isomer **22**. The structure of the trans double bond was indicated by the much larger coupling constant (J = 16 Hz) between the two trans protons in the ^1H NMR spectra of **19**, **20**, *trans*-**21**, and **22**. The structure of the terminal double bond of **23** was confirmed also by its coupling constant (J = 1.8 Hz) between the two methylidene protons in its ^1H NMR spectrum. The cis-disubstituted double bond of *cis*-**21** was supported by the characteristic coupling constant (J = 11.7 Hz) between the two cis-protons. The yields of these reactions were usually low (Scheme 7).

Scheme 7[a]



[a] Reagents and conditions: (i) $CH_2{=}CHCO_2Me$, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 100−120 °C, 5 h; (ii) $CH_2{=}CHCOMe$, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 100−120 °C, 5−10 h; (iii) $CH_2{=}CHCN$, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 110 °C, 11 h; (iv) $CH_2{=}CHPh$, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 100−120 °C.

Scheme 8



The reaction between areneboronic acid with aryl halide in the presence of Pd(0) catalyst, referred to as the Suzuki cross-coupling reaction,[26] proved to be a very efficient method for the synthesis of aryl-substituted pyrroles. In this connection, Suzuki coupling reaction[26] on pyrrole **11** was also performed. The cross-coupling proceeded smoothly in boiling toluene as solvent and $Pd(PPh_3)_4$ as catalyst. Sodium carbonate (2 equiv) as base was required to activate the palladium catalyst as well as the areneboronic acids. The results obtained from a variety of areneboronic acids are summarized in Scheme 8. Typically, the preparation of 1-(*tert*-butoxycarbonyl)-3-trimethylsilyl-4-phenyl-1*H*-pyrrole (**24**) in a moderate yield was based on the coupling of **11** with benzeneboronic acid. Compounds **25**, **26**, and **27** were obtained in a similar manner (Scheme 8).

Apart from the cross-coupling method, the iodo group of pyrrole **11** could also be converted to other substituents via an organometallic pathway.[31] For instance, **11** was able to undergo a rapid iodine−lithium exchange with *n*-BuLi in THF, which was followed by the quenching with H_2O to generate the corresponding 1-(*tert*-butoxycarbonyl)-3-trimethylsilyl-1*H*-pyrrole (**28**) (Scheme 9). It is believed that further manipulations of **28** may provide a useful access to 3-substituted-1*H*-pyrroles.

(27) Tao, W.; Nesbitt, S.; Heck, R. F. *J. Org. Chem.* **1990**, *55*, 63−69.

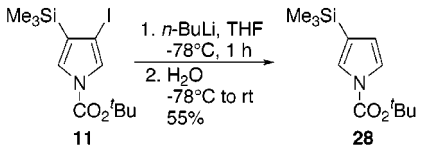
(28) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259−263.

(29) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1992**, *57*, 3558−3563.

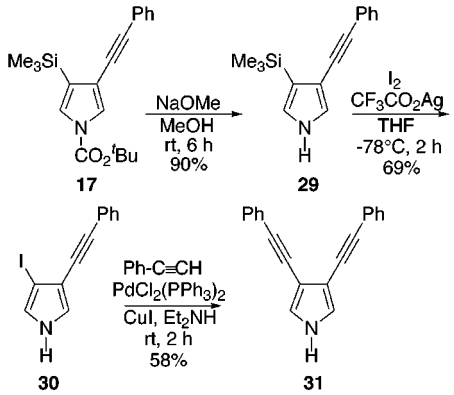
(30) Spencer, A. *J. Organomet. Chem.* **1983**, *258*, 101−108.

(31) Chen, W.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 6025−6026.

Scheme 9



Scheme 10

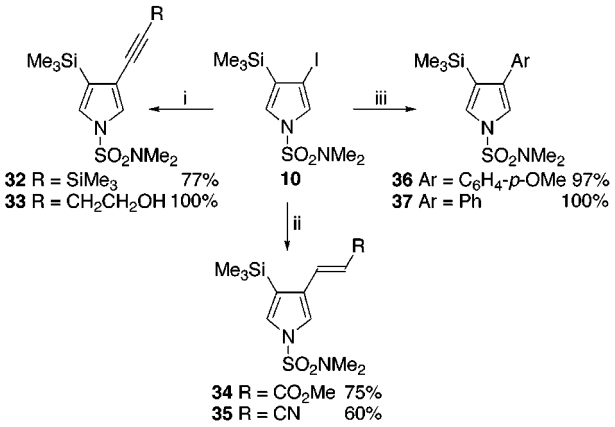


After the first trimethylsily group had been replaced by substituents, the remaining trimethylsilyl group of the 1-(*tert*-butoxycarbonyl)-protected pyrrole was subjected to a second ipso iodination. After that, a subsequent cross-coupling reaction might furnish ultimately 3,4-disubstituted 1*H*-pyrroles. Compound **17** was first chosen for further iodination. Nonetheless, the yields of the second iodination were not consistent, being frequently lower in large-scale iodination. In addition, the polarity of the starting material **17** was almost the same as that of the product, therefore making the chromatographic purification rather difficult. The reaction conditions (reaction time, solvent, temperature, silver catalyst) were modified all to no avail. An excess of iodine or prolonged reaction time only led to the decomposition of the starting materials. A similar result was also observed for the iodination of **24**.

In view of this unfavorable outcome, an alternative approach in which the order of functionalization was reversed was examined. Thus, **17** was first deprotected using NaOMe/MeOH to give 3-trimethylsilyl-4-phenylethynyl-1*H*-pyrrole (**29**). Without isolation, iodination of **29** was achieved following the aforementioned routine to afford **30**. Palladium-catalyzed cross-coupling of **30**, the final step toward the desired 3,4-disubstituted pyrroles, was successfully accomplished under the Sonogashira conditions[24] to provide 3,4-bis(phenylethynyl)-1*H*-pyrrole (**31**) (Scheme 10). It is noteworthy that **30** decomposed slowly upon purification on a silica gel column. For this reason, this strategy appeared to be quite limited in scope. At this juncture, a different approach was attempted and will be discussed in the following section.

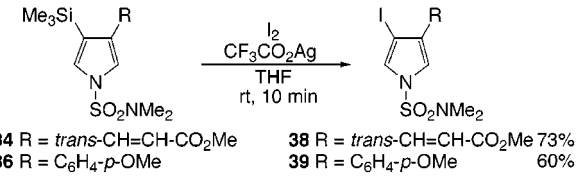
(b) 3,4-Disubstituted 1*H*-Pyrroles from *N*,*N*-Dimethyl-3-trimethylsilyl-4-iodo-1*H*-pyrrolesulfonamide (10). Since the introduction of the second iodine atom was apparently inaccessible in a clean manner via the 1-(*tert*-butoxycarbonyl)-protected pyrroles, we therefore turned our attention to other protecting groups with the conviction that 1-protecting groups could greatly influence pyrrole reactivities. Consequently, 1-(*N*,*N*-dimethylaminosulfonyl)-protecting pyrrole **10** was selected especially for the iodination of its remainimg trimethylsilyl group.

Scheme 11[a]



[a] Reagents and conditions: (i) RC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, rt, 7 h; (ii) CH_2=CHR, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 125 °C, 1 h; (iii) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, MeOH−PhMe, 90−100 °C, 12 h.

Scheme 12

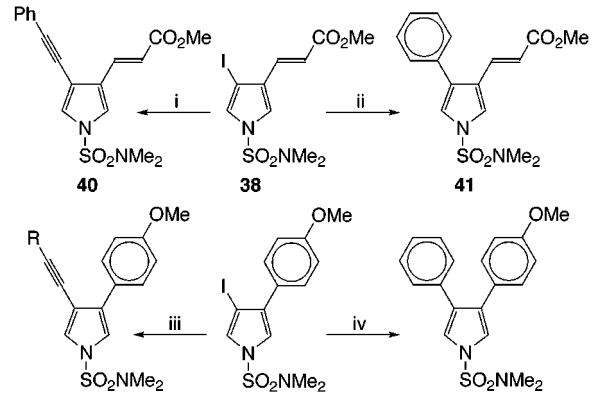


Reaction of pyrrole **10** with terminal acetylene under standard Sonogashira conditions[24] gave alkynylation products **32** and **33**. Pyrrole **10** was also able to couple with terminal alkenes to form exclusively trans-alkenylation products **34** and **35**.[25] Under Suzuki conditions,[26] the 4-aryl derivatives **36** and **37** were isolated in good yields after purification by chromatography (Scheme 11). The three types of palladium-catalyzed cross-couplings were found to go to completion in much shorter reaction times when compared to the 1-(*tert*-butoxycarbonyl) analogues.

The next step was again the ipso iodination of the remaining trimethylsilyl group. Although ipso iodinations of the first trimethylsilyl group in **4**−**8** were carried out at low temperatures (Scheme 4), the iodination of the second trimethylsilyl group of 1-(*N*,*N*-dimethylaminosulfonyl)-protected pyrroles must be performed at room temperature because of the strongly deactivating electron-withdrawing property of the *N*,*N*-dimethylsilylsulfonyl protecting group. Thus, treatment of the 4-alkenylpyrrole **34** with iodine and CF_3CO_2Ag at room temperature resulted in an ipso iodination, furnishing the iodide **38**. The 4-aryl derivative **36** reacted similarly to afford **39** (Scheme 12). No trace of starting **34** and **36** was observed on TLC plates, and the reactions were complete in a very short time.

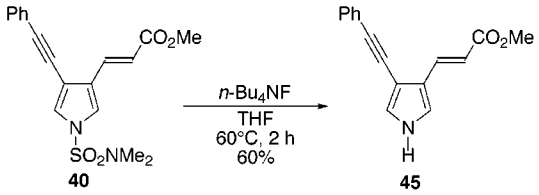
As expected, subsequent cross-coupling reactions proceeded very easily. For example, compound **38** was found to undergo alkynylation with phenylacetylene in 73% yield in 2−5 h at room temperature to afford **40**.[24] It also readily underwent a Suzuki coupling reaction[26] with benzeneboronic acid to give phenylpyrrole **41** in 78% yield. Likewise, compound **39** gave the corresponding trimethylsilylethyne and 4-hydroxybutyne derivative **42** and **43** in 90% and 80% yield, respectively. Diarylpyrrole **44** was isolated in 86% yield by reaction of **39** with benzeneboronic acid (Scheme 13).

Scheme 13[a]



[a] Reagents and conditions: (i) PhC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, rt, 2−5 h, 73%; (ii) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, MeOH−PhMe, 110 °C, 2 h, 78%; (iii) RC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, rt, 4 h, 80%; (iv) $PhB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, MeOH−PhMe, 110 °C, 1.5 h, 86%.

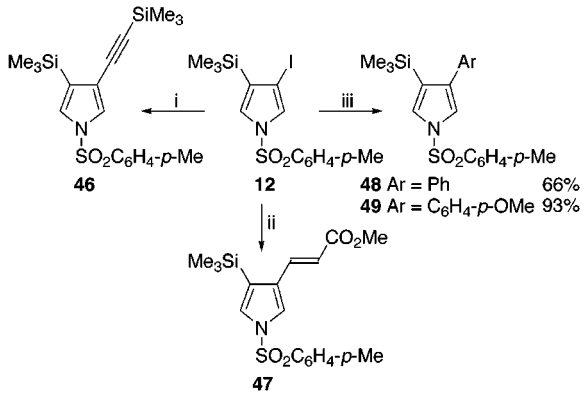
Scheme 14



The final step of our protocol required the deprotection of the *N*,*N*-dimethylaminosulfonyl group from pyrroles **40**−**44**. It is known that sulfonamides are among the most stable of the N-protecting groups, and their removal often requires drastic conditions, i.e., heating to reflux in a strong acid[32] or in a base.[33] In addition, the *N*,*N*-dimethylaminosulfonyl group is often used for imidazole protection,[34] and a survey of the literature revealed no example for pyrrole protection. Only very recently have some *N*-sulfonyl groups (*N*-methanesulfonyl, *N*-*p*-toluenesulfonyl, and *N*-benzenesulfonyl) on pyrroles and indoles been reported to be cleaved with TBAF in THF.[35] Some other milder deprotection methods for *N*-sulfonyl groups, such as Mg/MeOH[36] or NaI/Me_3SiCl,[37] were also recorded. However, treatment of the *N*,*N*-dimethylaminosulfonyl-protected pyrroles **40**−**44** with 2 equiv of TBAF in THF at 60−70 °C failed to afford the desired parent 3,4-disubstituted 1*H*-pyrroles except for **40**, which generated nonprotected **45** (Scheme 14). For the other four protected pyrroles **41**−**44**, alternate deprotection procedures involving Mg/MeOH or NaI/Me_3SiCl were also unfruitful.

(c) 3,4-Disubstituted 1*H*-Pyrroles from 1-(*p*-Toluenesulfonyl)-3-trimethylsilyl-4-iodo-1*H*-pyrrole (12). The difficulties associated with the deprotection of *N*,*N*-dimethylaminosulfonyl group led us to examine other protecting groups. A careful literature search revealed that the *p*-toluenesulfonyl group appeared to be a good substitute for the *N*,*N*-dimethylaminosulfonyl group. The choice in favor of the *p*-toluenesulfonyl group as the 1-protecting group was due to the fact that an electron-withdrawing *p*-toluenesulfonyl group, like the *N*,*N*-dimethylaminosulfonyl group, should benefit the Heck reaction as well as iodination reactions when compared with the *tert*-butoxycarbonyl series. Moreover, unlike the *N*,*N*-dimethylaminosulfonyl group, the *p*-toluenesulfonyl group was often used for pyrrole protection, and because of this a number of methods are available for its removal.[38]

Scheme 15[a]



[a] Reagents and conditions: (i) $Me_3SiC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, rt, 14 h, 94%; (ii) $CH_2{=}CHCO_2Me$, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 100−120 °C, 1 h, 94%; (iii) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, MeOH−PhMe, 100−110 °C, 3 h.

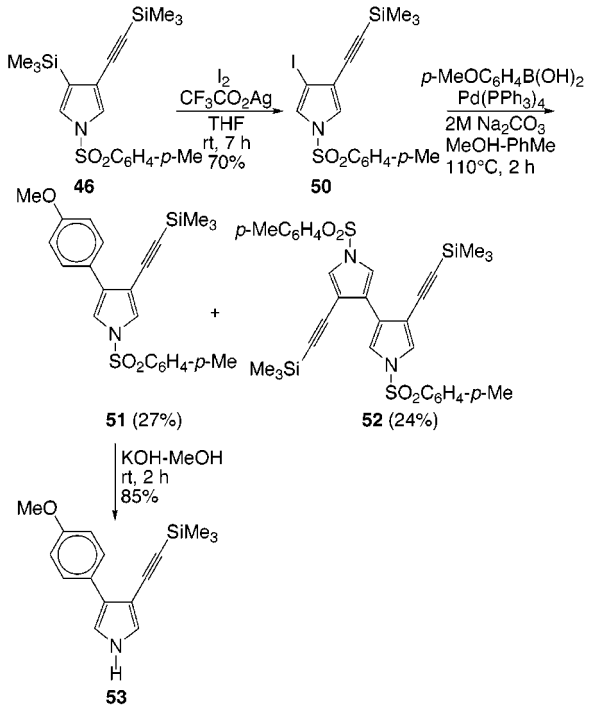
The same synthetic strategy used for 1-(*N*,*N*-dimethylaminosulfonyl)-3,4-disubstituted-1*H*-pyrroles was carried out. Thus, iodopyrrole **12** was converted to alkynylated product **46** under standard Sonogashira conditions.[24] The 3-alkenylated **47** and 3-arylated derivatives **48** and **49** were also readily obtained through Heck[25] and Suzuki[26] reactions in good yield, respectively (Scheme 15).

Similar to 1-(*N*,*N*-dimethylaminosulfonyl)-protected pyrroles, the iodination of the remaining trimethylsilyl group of **46** gave iodide **50** in a reasonable yield and in a clean manner. As discussed previously, the displacement of the second trimethylsilyl always required a much higher reaction temperature than that of the first trimethylsilyl group. This particular characteristic is essential to our program because only in this way unsymmetrically 3,4-disubstituted 1*H*-pyrroles can be realized. Compound **50** reacted with *p*-methoxybenzeneboronic acid under Suzuki conditions[26] to afford two products, namely the normal 3,4-disubstituted 1-(*p*-toluenesulfonyl)pyrrole **51** and the undesired bipyrrole **52**. As predicted previously, the *p*-toluenesulfonyl group was easily removed by treatment of **51** with KOH in MeOH, giving **53** in good yield (Scheme 16). On the other hand, **47** was converted to **55** via **54** in a simple manner (Scheme 17).

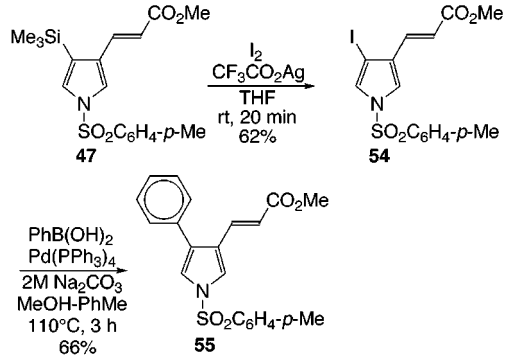
From the iodinated compound **56**, obtained in turn from **48**, two 1-(*p*-toluenesulfonyl)-3,4-disubstituted pyrroles **55** and **57** were obtained through Heck[25] and Suzuki[26] reactions, respectively (Scheme 18). Deprotection of these 1-(*p*-toluenesulfonyl)-protected pyrroles was

(32) Snyder, H. R.; Heckert, R. E. *J. Am. Chem. Soc.* **1952**, *74*, 2006−2009.
(33) Sundberg, R. J.; Laurino, J. P. *J. Org. Chem.* **1984**, *49*, 249−254.
(34) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351−2358.
(35) Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595−596.
(36) Okabe, K.; Natsume, M. *Tetrahedron* **1991**, *47*, 7615−7624.
(37) Sabitha, G.; Subba Reddy, B. V.; Abraham, S.; Yadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 1569−1570.
(38) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994; pp 209−215.

Scheme 16



Scheme 17



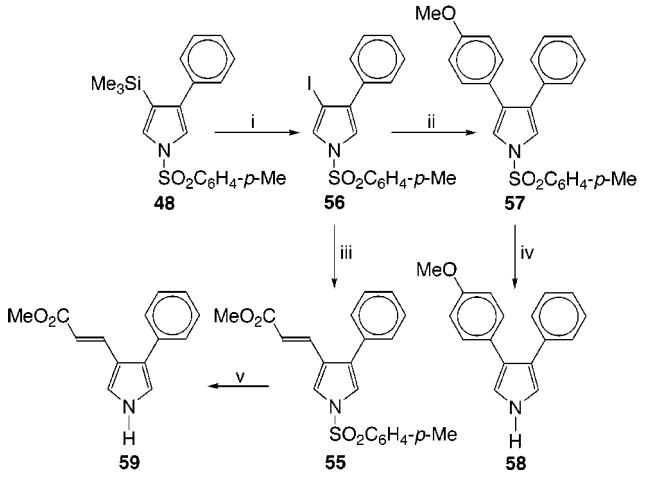
accomplished successfully. The *p*-toluenesulfonyl group was removed by treatment of **57** with KOH in MeOH to afford **58** (Scheme 18). In order not to affect the methoxycarbonyl, the protecting group of **55** was removed to afford **59** under a milder condition, i.e., TBAF in THF with heating at 60−70 °C (Scheme 18).

(d) 3,4-Disubstituted 1*H*-Pyrroles from 1-Triisopropylsilyl-3-trimethylsilyl-4-bromo-1*H*-pyrrole (60). Although our initial plan to secure unsymmetrically 3,4-disubstituted 1*H*-pyrroles by starting from the 1-(*p*-toluenesulfonyl)-protected pyrroles was successful, we also investigated the use of triisopropylsilyl as a protecting group in the synthesis of 3,4-disubstituted-1*H*-pyrroles. In addition to the ipso iodination that afforded **9**, the trimethylsilyl group of **4** was also efficiently replaced by a bromo group through the reaction with NBS at −10 °C (Scheme 19), providing bromide **60**.

Lithiation of **60** at −78 °C and subsequent quenching with either iodomethane or benzaldehyde gave **61** (60%) and **62** (21%), respectively (Scheme 20).

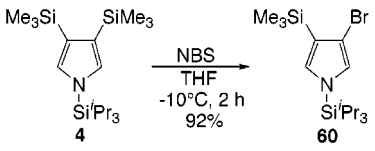
As shown in Scheme 21, pyrrole **61** underwent further regiospecific iodination at room temperature to yield iodide **63**, from which several palladium-catalyzed cross-coupling reactions were carried out. For instance, com-

Scheme 18[a]

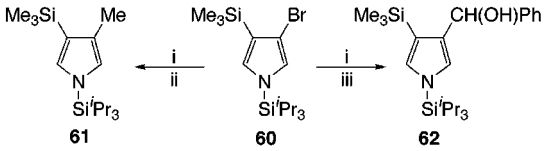


[a] Reagents and conditions: (i) I_2, CF_3CO_2Ag, THF, rt, 1 h, 62%; (ii) *p*-MeOC6H4B(OH)2, $Pd(PPh_3)_4$, 2 M Na_2CO_3, MeOH−PhMe, 100 °C, 2.5 h, 37%; (iii) $CH_2{=}CHCO_2Me$, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 100 °C, 50 min, 66%; (iv) KOH, MeOH, rt, 1 h, 95%; (v) *n*-Bu4NF, THF, 60 °C, 3 h, 96%.

Scheme 19

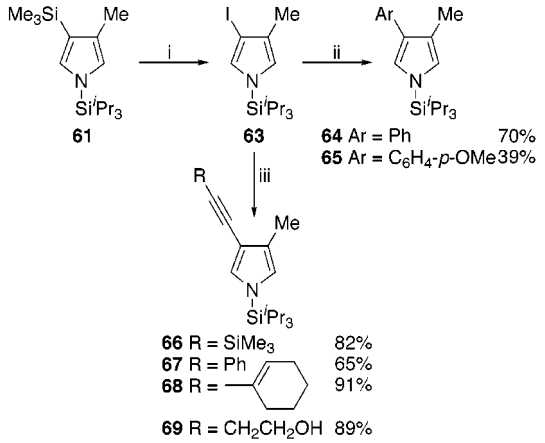


Scheme 20[a]



[a] Reagents and conditions: (i) *n*-BuLi, THF, HMPA, −78 °C; (ii) MeI, −78 °C, 60%; (iii) PhCHO, −78 °C, 21%.

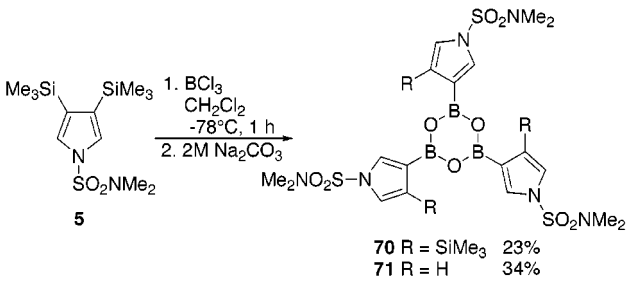
Scheme 21[a]



[a] Reagents and conditions: (i) I_2, CF_3CO_2Ag, THF, rt, 55%; (ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 M Na_2CO_3, MeOH−PhMe, 80 °C; (iii) RC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_2NH, rt.

pounds **64** and **65** were obtained from **63** via a Suzuki reaction pathway.[26] It is interesting to note that the unprotected **64**, namely 3-phenyl-4-methyl-1*H*-pyrrole, was recently isolated from the cephalic extracts of the ant *Anochetus kempfi*.[39] Sonogashira reaction[24] of **63** with

Scheme 22



four different terminal alkynse gave pyrroles **66**−**69**, respectively. Unfortunately, all attempts to react **63** under a variety of Heck reaction conditions[25] failed.

Under usual workup procedures, it was observed that all the triisopropylsilyl-protected pyrroles are relatively less stable, as compared with their less electron-rich analogues mentioned above. For example, the 1-triisopropylsilylpyrroles must be chromatographed on silica gel columns in the presence of Et_3N. A neat sample of **63** even turned dark upon keeping at room temperature.

4. Synthesis of Pyrroleboroxines. 3,4-Bis(trimethylsilyl)furan (**1**) was successfully converted to its boroxine, which was used as a key intermediate for the realization of many 3,4-disubstituted furans.[13] According to the literature method,[13] the reaction was performed by adding BCl_3 to a CH_2Cl_2 solution of the acid-sensitive pyrrole **3**. However, it was observed that the reaction solutions immediately darkened as BCl_3 was slowly added to pyrroles **3** or **4** even at −78 °C. When 1-(*tert*-butoxycarbonyl)-protected pyrrole **6** was used, the situation was improved to a certain extent in that only at approximately 0 °C did the solution turned dark. The protecting groups on the pyrroles apparently were able to moderate their reactivities. In this connection, an obvious choice would be the *N*,*N*-dimethylaminosulfonyl-protected pyrrole **5**. Therefore, pyrrole **5** was allowed to react with BCl_3 in a dilute CH_2Cl_2 solution at −78 °C. After usual workup and purification by column chromatography, **70** was obtained in a meager 23% yield, together with a significant amount of **71** (34%) (Scheme 22). Due to its disappointing yield, it was concluded that **70** was not a suitable precursor for the synthesis of 3,4-disubstituted-1*H*-pyrrole.

Conclusion

Triisopropylsilyl, *tert*-butoxycarbonyl, *p*-toluenesulfonyl, and *N*,*N*-dimethylaminosulfonyl were introduced to the pyrrole nitrogen of **3** as protecting groups. 3,4-Disubstituted 1*H*-pyrroles were synthesized through stepwise and repeated iodination and palladium-catalyzed cross-coupling reaction. Three drawbacks were encountered in this study, namely, the Heck coupling reaction, the ipso iodination to replace the second trimethylsily group, and the final deprotection step. Of several alternatives we investigated, the *tert*-butoxycarbonyl group was unfavored both for the Heck reaction and for the ipso iodination. The *N*,*N*-dimethylaminosulfonyl group gave acceptable results not only for the Heck coupling but also for the ipso iodination. Nevertheless, the deprotection of the *N*,*N*-dimethylaminosulfonyl group was performed with great difficulties. Despite this discrepancy, the *N*,*N*-dimethylaminosulfonyl group can still serve as a good 1-protecting group for access to 3,4-disubstituted 1*H*-pyrroles when a more effective deprotection condition is uncovered. The *p*-toluenesulfonyl group is by far the best protection group that led to various parent 3,4-disubstituted 1*H*-pyrroles. The advantages of the *p*-toluenesulfonyl over triisopropylsilyl, *tert*-butoxycarbonyl, and *N*,*N*-dimethylaminosulfonyl are evident because it was compatible with easy experimental manipulation, reliable large-scale operation, and chromatographic stability on silica gel.

Experimental Section

1-Triisopropylsilyl-3,4-bis(trimethylsilyl)-1*H*-pyrrole (4). *n*-BuLi (1 mL, 1.6 mmol) was added to a stirred solution of pyrrole **3**[14] (0.3 g, 1.42 mmol) in THF (6.5 mL) at −78 °C. Twenty minutes later, triisopropylsilyl chloride (0.3 mL, 1.42 mmol) was added and stirred for another 30 min. The reaction mixture was warmed to room temperature over 15 min. Usual workup (Et_2O) gave **4** as a colorless oil (495 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 18H), 1.09 (d, J = 7.4 Hz, 18H), 1.43 (sept, J = 7.4 Hz, 3H), 6.88 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 1.03, 11.87, 17.90, 123.52, 133.58; MS *m*/*z* 367 (M^+, 82); HRMS calcd for $C_{19}H_{41}NSi_3$ 367.2541, found 367.2552.

***N*,*N*-Dimethyl 3,4-Bis(trimethylsilyl)-1*H*-pyrrole-1-sulfonamide (5).** NaH (1.44 g, 36 mmol) was placed in a 250 mL three-necked flask fitted with a thermometer, and a dropping funnel and was washed with hexanes (2 × 8 mL). Then DMF (70 mL) was added. This NaH−DMF mixture was cooled to 0 °C, and a solution of **3** (6.33 g, 30 mmol) in DMF (50 mL) was added dropwise. After addition, the reaction was stirred at 0 °C for 2 h. $ClSO_2NMe_2$ (3.22 mL, 30 mmol) in DMF (50 mL) was added, and the mixture was stirred and simultaneously allowed to warm to room temperature in 2 h. The resulting mixture was then poured into ice−water (250 mL), and Et_2O (300 mL) was added. The aqueous layer was separated and washed with Et_2O (2 × 200 mL). The combined ethereal solution was washed with water (2 × 200 mL) and brine (2 × 200 mL) and dried over $MgSO_4$. After evaporation, the residue was purified by chromatography on silica gel (400 g) eluted with hexanes/Et_2O (10:1) to give **5** (9.27 g, 97%) as white crystals: mp 109 °C; ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 18H), 2.81 (s, 6H), 7.14 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 0.51, 38.29, 125.89, 128.94; MS *m*/*z* 318 (M^+, 55). Anal. Calcd for $C_{12}H_{26}N_2O_2SSi_2$: C, 45.24; H, 8.23; N, 8.79. Found: C, 45.20; H, 8.49; N, 8.85.

Deprotection of 1-(*tert*-Butoxycarbonyl)-3,4-bis(trimethylsilyl)-1*H*-pyrrole (6). A mixture of **6**[14] (31 mg, 0.1 mmol) and NaOMe (11 mg, 0.2 mmol) in MeOH (3 mL) was stirred at room temperature for 8 h to give white solids (17 mg, 80%): mp 115−118 °C; The ^{1}H NMR spectrum was identical to that of an authentic sample of **3**.[14]

Deprotection of 1-(*p*-Toluenesulfonyl)-3,4-bis(trimethylsilyl)-1*H*-pyrrole (7). KOH (100 mg) was added to a solution of **7**[14] (13.9 mg, 0.04 mmol) in MeOH (1.5 mL). The mixture was stirred at room temperature for 20 h. After extraction with Et_2O (10 mL), washing with H_2O (5 mL), drying (Na_2SO_4), filtration, and evaporation, the pale yellow residue was crystallized from MeOH−H_2O (5:1) to afford white crystals (5 mg, 62%): mp 115−118 °C. The ^{1}H NMR spectrum was identical to that of an authentic sample of **3**.[14]

1-(*tert*-Butyl)-3,4-bis(trimethylsilyl)-1*H*-pyrrole (8). To a solution of 1-(*tert*-butyl)-2-aziridinecarbonitrile[16] (436 mg, 3.5 mmol) in xylene (18 mL) was added bis(trimethylsilyl)acetylene (780 mg, 4.6 mmol) at room temperature. This mixture was refluxed under N_2 for 18 h. The solvent was evaporated in vacuo. The residue was taken up in Et_2O, and the resulting ethereal solution was filtered through Celite (2 cm). The filtrate was concentrated and chromatographed on silica gel (150 g) eluted with hexanes/Et_2O (20:1) to afford **8** (744 mg, 79%) as colorless crystals: ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 18H), 1.54 (s, 9H), 6.95 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 1.33, 30.91, 54.68,

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121.11, 127.29; MS *m/z* 267(M^+, 77). Anal. Calcd for $C_{14}H_{29}NSi_2$: C, 62.85; H, 10.92; N, 5.23. Found: C, 62.85; H, 11.23; N, 4.94.

1-Triisopropylsilyl-3-trimethylsilyl-4-iodo-1*H*-pyrrole (9). (Representative Example of Iodination: Procedure 1). A mixture of pyrrole **4** (73.4 mg, 0.2 mmol) and CF_3CO_2Ag (44 mg, 0.2 mmol) dissolved in THF (5 mL) was cooled to −78 °C, and I_2 (50.8 mg, 0.2 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C under N_2. The brown mixture was diluted with Et_2O (10 mL) and then filtered through Celite. The filteration was washed successively with 50% aqueous $Na_2S_2O_3$ (3 × 5 mL), H_2O (10 mL), and brine (10 mL) and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography (silica gel, 20 g) with hexanes as eluent to give **9** (72 mg, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.28 (s, 9H), 1.08 (d, J = 7.4 Hz, 18H), 1.42 (sept, J = 7.4 Hz, 3H), 6.62 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −0.57, 11.62, 17.75, 68.85, 123.28, 130.68, 131.73; MS *m/z* 421 (M^+, 12); HRMS calcd for $C_{16}H_{32}INSi_2$ 421.1112, found 421.1102.

3-Trimethylsilyl-4-cyano-1*H*-pyrrole (14). A mixture of **11** (365 mg, 1 mmol), KCN (130 mg, 2 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), KOH (8.4 mg, 0.15 mmol), and HMPA (5 mL) was heated at 75 °C for 12 h under N_2. After extraction with EtOAc (2 × 20 mL), the organic layer was washed with H_2O (35 mL), dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed (hexanes/Et_2O 1:1) on silica gel (40 g) to afford **14** (90 mg, 55%) as colorless crystals: ^{1}H NMR ($CDCl_3$) δ 0.30 (s, 9H), 6.79 (t, J = 1.8 Hz, 1H), 7.41 (d, J = 1.8 Hz, 1H), 9.30 (s, br, 1H); ^{13}C NMR ($CDC1_3$) δ −0.93, 96.71, 118.15, 121.53, 124.99, 127.97; MS *m/z* 164 (M^+, 49); HRMS calcd for $C_8H_{13}N_2Si$ (MH^+) 165.0842, found 165.0841.

1-(*tert*-Butoxycarbonyl)-3-trimethylsilyl-4-trimethylsilylethynyl-1*H*-pyrrole (15). (Representative Example of Sonogashira Reaction: Procedure 2). $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) and CuI (114 mg, 0.6 mmol) were added to a solution of pyrrole **11** (365 mg, 1 mmol), trimethylsilylacetylene (156 mg, 1.6 mmol), and Et_2NH (3 mL). This mixture was stirred for 24 h at room temperature under N_2. The solvent was evaporated, and the residue was purified by chromatography on silica gel (20 g, hexanes) to give **15** (307 mg, 92%) as colorless crystals: mp 48−49 °C; ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 9H), 0.28 (s, 9H), 1.59 (s, 9H), 7.12 (d, J = 1.8 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.25, −0.14, 27.85, 84.10, 95.32, 100.49, 112.40, 124.80, 125.33, 147.96; MS *m/z* 335 (M^+, 17). Anal. Calcd for $C_{17}H_{29}NO_2Si_2$: C, 60.84; H, 8.71; N, 4.17. Found: C, 60.76; H, 9.01; N, 4.09.

1-(*tert*-Butoxycarbonyl)-3-trimethylsilyl-4-(*trans*-2-methoxycarbonylethenyl)-1*H*-pyrrole (19). (Representative Example of Heck Coupling Reaction: Procedure 3). To a solution of **11** (365 mg, 1.0 mmol) in DMF (9 mL) were added methyl acrylate (1.25 mL, 13.8 mmol), Et_3N (4 mL), and $PdCl_2(PPh_3)_2$ (100 mg, 0.14 mmol) at room temperature. The reaction mixture was refluxed at 100−120 °C under N_2 with stirring for 5 h. After extraction with Et_2O (2 × 20 mL), washing with H_2O (15 mL), drying (Na_2SO_4), filtration, and evaporation, the residue was chromatographed (hexanes/EtOAc 5:2) on silica gel (40 g) to give **19** (107 mg, 33%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H), 1.59 (s, 9H), 3.76 (s, 3H), 6.19 (d, J = 15.9 Hz, 1H), 7.20 (d, J = 1.8 Hz, 1H), 7.58 (d, J = 2.1 Hz, 1H), 7.61 (d, J = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −0.41, 27.85, 51.42, 84.43, 116.33, 121.43, 122.35, 127.29, 138.90, 148.07, 167.62; MS *m/z* 323 (M^+, 3). Anal. Calcd for $C_{16}H_{25}NO_4Si$: C, 59.41; H, 7.79; N, 4.33. Found: C, 59.34; H, 8.04; N, 4.30.

1-(*tert*-Butoxycarbonyl)-3-trimethylsilyl-4-phenyl-1*H*-pyrrole (24). (Representative Example of Suzuki Coupling Reaction: Procedure 4). To a solution of **11** (365 mg, 1 mmol), benzeneboronic acid (122 mg, 1 mmol), and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in MeOH−toluene (1:1, 3 mL) was added a 2 M Na_2CO_3 solution (0.4 mL). The resulting mixture was heated at ca. 100 °C for 4 h and then poured into ice−water (10 mL). After extraction with Et_2O (2 × 20 mL), washing with H_2O (15 mL), drying (Na_2SO_4), filtration, and evaporation, the residue was chromatographed (1% Et_2O in hexanes) on silica gel (40 g) to give **24** (189 mg, 60%) as colorless crystals: ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 9H), 1.60 (s, 9H), 7.26−7.37 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 0.07, 27.99, 83.72, 118.76, 121.85, 126.73, 126.93, 128.02, 128.69, 133.67, 136.72, 148.69; MS *m/z* 315 (M^+, 8). Anal. Calcd for $C_{18}H_{25}NO_2Si$: C, 68.53; H, 7.99; N, 4.44. Found: C, 68.75; H, 8.22; N, 4.43.

1-(*tert*-Butoxycarbonyl)-3-trimethylsilyl-1*H*-pyrrole (28). (Representative Example of Lithiation and Subsequent Nucleophilic Substitution: Procedure 5). To a stirred solution of **11** (365 mg, 1 mmol) in dry THF (16 mL) was added dropwise *n*-BuLi (0.75 mL, 1.2 mmol), and the mixture was stirred for 1 h at −78 °C under N_2. H_2O (54 mL, 3 mmol) was added, and the mixture was stirred for an additional 3.5 h until warmed to room temperature. After extraction with Et_2O (2 × 20 mL), washing with H_2O (15 mL), drying (Na_2SO_4), filtration, and evaporation, the residue was chromatographed (hexane/CH_2Cl_2 30:4) on silica gel (40 g) to give **28** (132 mg, 55%) as a colorless residue: ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 1.59 (s, 9H), 6.25 (dd, J = 3.0, 1.5 Hz, 1H), 7.24 (d, J = 1.5 Hz, 1H), 7.28−7.29 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −0.73, 27.90, 83.36, 115.95, 120.97, 122.09,125.15, 148.73; MS *m/z* 239 (M^+, 22); HRMS calcd for $C_{12}H_{21}NO_2Si$ (MH^+) 240.1414, found 240.1412.

3-Iodo-4-phenylethynyl-1*H*-pyrrole (30). A mixture of **17** (335 mg, 1 mmol) and NaOMe (0.2 g) was dissolved in MeOH (5 mL) and stirred at room temperature for 6 h. After washing (H_2O), extraction (Et_2O), and evaporation, the residue was flash chromatographed (hexane/Et_2O 5:2) on silica gel (5 g) to afford **29** as a brown sticky oil, which was used without further purification and identification. Compound **29** was dissolved in THF (30 mL) and iodinated with I_2 (400 mg, 1.57 mmol) and CF_3CO_2Ag (363 mg, 1.65 mmol) at −78 °C for 2 h. The crude residue was purified by chromatography on silica gel (40 g, hexane/Et_2O 7:2) to afford **30** (181 mg, 62% over two steps) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 6.83 (t, J = 2.4 Hz, 1H), 7.02 (t, J = 2.4 Hz, 1H), 7.32−7.58 (m, 5H), 8.39 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 67.25, 84.04, 90.80, 110.75, 122.33, 123.27, 123.64, 127.79, 128.25, 131.31; MS *m/z* 293 (M^+, 100). Anal. Calcd for $C_{12}H_8IN$: C, 49.17; H, 2.75; N, 4.78. Found: C, 49.15; H, 2.64; N, 4.67.

3-Phenylethynyl-4-(*trans*-2-methoxycarbonylethenyl)-1*H*-pyrrole (45). A solution of **40** (36 mg, 0.1 mmol), TBAF (0.2 mL, 0.2 mmol), and THF (3 mL) was stirred at 60 °C for 2 h. After extraction with EtOAc (2 × 10 mL), washing with H_2O (10 mL), drying (Na_2SO_4), filtration, and evaporation, the residue was chromatographed (hexane/EtOAc 4:1) on silica gel (20 g) to afford **45** (21 mg, 60%) as a yellow residue: ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 6.82 (d, J = 15.9 Hz, 1H), 6.99 (t, J = 2.4 Hz, 1H), 7.07 (t, J = 2.4 Hz, 1H), 7.33−7.37 (m, 3H), 7.51−7.54 (m, 2H), 7.72 (d, J = 15.9 Hz, 1H), 8.75 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 51.46, 83.44, 91.79, 104.19, 114.47, 121.01, 121.09, 123.66, 124.22, 127.86, 128.34, 131.18, 137.67, 168.76; MS *m/z* 251 (M^+, 12). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.22; H, 5.28; N, 5.37.

3-(*p*-Methoxyphenyl)-4-trimethylsilylethylnyl-1*H*-pyrrole (53). Pyrrole **51** (42 mg, 0.1 mmol) was dissolved in THF (2 mL) and MeOH (2 mL) containing KOH (0.2 g) at room temperature for 2 h. The reaction was quenched by pouring into H_2O (15 mL) and extracted with Et_2O (15 mL). The residue after evaporation was chromatographed on silica gel (15 g) eluted by hexane/Et_2O (5:2) to give **53** (23 mg, 85%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.33 (s, 9H), 3.82 (s, 3H), 6.74 (t, J = 2.1 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 2.1 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 8.37 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ −0.70, 55.26, 84.47, 88.75, 109.41, 113.89, 116.63, 120.58, 123.16, 123.96, 132.32, 158.90; MS *m/z* 269 (M^+, 100). Anal. Calcd for $C_{16}H_{19}NOSi$: C, 71.33; H, 7.11; N, 5.20. Found: C, 71.55; H, 7.41; N, 5.16.

3-(*p*-Methoxyphenyl)-4-phenyl-1*H*-pyrrole (58). This compound was prepared from **57** (161 mg, 0.4 mmol) and KOH (0.5 g) in a similar manner as described for **53** and purified by chromatography on silica gel (25 g) eluted with hexanes/Et_2O (5:2) to afford **58** (95 mg, 95%) as a yellow residue: ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.90−6.96 (m, 4H), 7.26−7.40 (m, 7H), 8.38 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 55.13, 113.59, 116.97,

117.23, 122.98, 123.24, 125.57, 128.12, 128.25, 128.41, 129.58, 135.81, 157.74; MS *m*/*z* 249 (M^+, 100); HRMS calcd for $C_{17}H_{15}NO$ 249.1148, found 249.1129.

3-Phenyl-4-(*trans*-2-methoxycarbonylethenyl)-1*H*-pyrrole (59). Pyrrole **55** (191 mg, 0.5 mmol) was deprotected with TBAF (1 mL, 1 mmol) in the same manner as that for **40** and purified by chromatography on silica gel (25 g) eluted with hexanes/EtOAc (25:6) to give **59** (109 mg, 96%) as a yellow residue: ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 6.12 (d, J = 15.9 Hz, 1H), 6.84 (t, J = 2.4 Hz, 1H), 7.18 (t, J = 2.4 Hz, 1H), 7.29−7.43 (m, 5H), 7.76 (d, J = 15.9 Hz, 1H), 8.67 (s, br, 1H); ^{13}C NMR (d_6-acetone) δ 50.86, 113.03, 117.87, 118.71, 121.04, 125.84, 126.67, 128.96, 129.24, 136.15, 139.30, 168.04; MS *m*/*z* 227 (M^+, 17). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.71; H, 5.76; N, 6.05.

1-Triisopropylsilyl-3-trimethylsilyl-4-bromo-1*H*-pyrrole (60).[8h] To a solution of **4** (36.7 mg, 0.1 mmol) in THF (2 mL) was added solid NBS (17.8 mg, 0.1 mmol) under N_2 at −10 °C, and the mixture was stirred for 2 h. After that, aqueous 50% $Na_2S_2O_3$ (3 mL) and Et_2O (15 mL) were added. The ethereal layer was separated, washed with H_2O (2 × 5 mL), and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (20 g, hexanes) to give **60** (34.4 mg, 92%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H), 1.09 (d, J = 7.4 Hz, 18H), 1.40 (sept, J = 7.4 Hz, 3H), 6.61 (d, J = 2.2 Hz, 1H), 6.79 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 0.63, 11.56, 17.73, 103.97, 120.21, 124.78, 130.69; MS *m*/*z* 375 (M^+, 70).

Tris[1-(*N*,*N*-dimethylaminosulfonyl)-4-trimethylsilyl-1*H*-pyrrol-3-yl]boroxine (70) and Tris[1-(*N*,*N*-dimethylaminosulfonyl)-1*H*-pyrrol-3-yl]boroxine (71). To a solution of **5** (637 mg, 2 mmol) in CH_2Cl_2 (80 mL) was added a solution of BCl_3 (2 mL) diluted with CH_2Cl_2 (35 mL) under N_2 at −78 °C. After the temperature was raised to 0 °C (ca. 6 h), the reaction was quenched with H_2O. After the usual workup (Et_2O), the residue was subjected to silica gel (60 g) chromatography with hexanes/Et_2O (1:1) as the eluent. The first fraction contained 125 mg (23%) of white solids identified as **70**: mp 247 °C; ^{1}H NMR ($CDCl_3$) δ 0.41 (s, 9H), 2.85 (s, 6H), 7.13 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −0.30, 38.33, 119.16, 126.75, 128.08, 135.78. Boroxine **70** was not too stable for further identification. The second fraction contained 134 mg (34%) of white solids identified as **71**: mp 210 °C; ^{1}H NMR ($CDCl_3$) δ 2.84 (s, 18H), 6.80 (dd, J = 3.0, 2.4 Hz, 3H), 7.16 (dd, J = 3.0, 2.4 Hz, 3H), 7.77 (t, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 38.31, 115.60, 116.72, 121.79, 131.24; MS *m*/*z* 600 (M^+, 100). Anal. Calcd for $C_{18}H_{27}B_3N_6O_9S_3$: C, 35.99; H, 4.53; N, 14.00. Found: C, 35.91; H, 4.62; N, 13.82.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for the compounds prepared as well as the experimental procedures for the preparation of **10**−**13**, **16**−**18**, **20**−**23**, **25**−**27**, **31**−**44**, **46**−**52**, **54**−**57**, and **61**−**69**. This material is available free of charge via the Internet at http://pubs.acs.org.

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