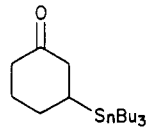
Me_3Sn and Bu_3Sn are tolerated.

Interestingly, steric crowding in the enone was not a problem as illustrated by additions to 3-methylcyclohexenone and 4,4-dimethylcyclohexenone. In these reactions **2b** and **2c** were formed in high yield, but longer reaction times were required. The efficient preparation of **2b** was especially noteworthy as a quaternary carbon was generated.

The reactions of **2** have not yet been fully explored; however, simple desilylation with tetrabutylammonium fluoride gives **3**, which has previously been prepared by



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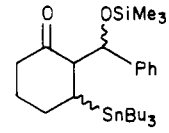

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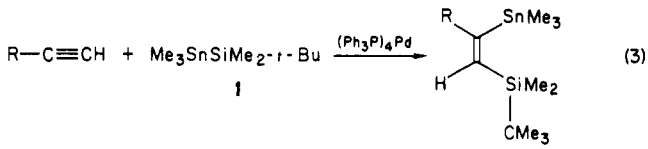
conjugate addition of Bu_3SnLi to cyclohexenone.[1b] We also find that fluoride-catalyzed aldol condensation with benzaldehyde under conditions similar to those of Noyori[12] is efficient providing **4** in 60% yield as a 1:1 mixture of *threo* and *erythro* isomers.

The silylstannylation of acetylenes was also examined. We reacted **1** (R_3 = Me_3; R^1_3 = *t*-$BuMe_2$) with phenylacetylene in the presence of catalytic tetrakis(triphenylphosphine)palladium in THF solution.[13] Within 4–8 h at 65 °C the starting materials were consumed, and the adduct **5a** was obtained in 90% yield upon Kugelrohr distillation (eq 3).[14] This addition was regio- and stereoselective with the ^{119}Sn and ^{117}Sn couplings to the vinyl proton (182 and 174 Hz, respectively) being diagnostic.[13b]

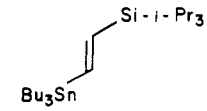


(3)

5a, R = Ph (93%)
b, R = $CH_3(CH_2)_3$ (74%)
c, R = *i*-Pr (67%)
d, R = *t*-Bu (10%)
e, R = $NC(CH_2)_3$ (90%)

Silylstannylation of terminal acetylenes appears to be quite general, though we have not examined many functionalized molecules. Note that a cyanoalkyl side chain (**5e**) was tolerated. A *tert*-butyl substituent appears to retard the addition as indicated by the low yield of adduct **5d**.

In conclusion, we have demonstrated that the readily available silylstannanes are useful reagents for the bis functionalization of α,β-unsaturated ketones and terminal acetylenes. The adducts obtained may serve as intermediates for a variety of useful transformations. For example, a trans silyl tin olefin (**6**)[15] has found great utility as an intermediate in Denmark's silicon-directed Nazarov cyclization reaction.[15,16] We envision a similar application for **5**.



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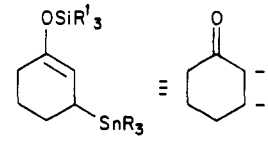
We are presently developing a protocol to use **2** as a synthon for an α,β-dianion of a ketone (eq 4) where the nucleophilicity of the α and β sites in the ketone may be expressed by means not presently available. This new



(4)

2

methodology should nicely compliment the tandem Michael addition–alkylation (aldol) sequence afforded by conventional organometallic chemistry.[17,18]

Acknowledgment. The fine technical assistance of D. R. Sanderson is gratefully acknowledged.

† Contribution #3791 from the Department.

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(14) The synthesis of **5a** was typical. Phenyl acetylene (3.25 g, 29.7 mmol) and (*tert*-butyldimethylsilyl)trimethylstannane (8.27 g, 29.7 mmol) were dissolved in dry THF (30 mL) in a dry flask with magnetic stirrer under a nitrogen atmosphere. Tetrakis(triphenylphosphine)palladium (100 mg) was added, and the mixture was refluxed gently for 6 h. The solvent was removed at reduced pressure, and the crude product was Kugelrohr distilled [100 °C (0.1 mm) pot temperature] to give 10.6 g, 93%, of **5a** as a white solid, mp 47–78 °C.

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(18) As this stage of our work was completed the reaction of silyl stannanes with acetylenes was independently discovered by Mitchell and co-workers. Mitchell, T. N.; Killing, H.; Dicke, R.; Wickenkamp, R. *J. Chem. Soc., Chem. Commun.* **1985**, 345–355.

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Synthetic Application of Photochemical Electron Transfer to Direct Amination of Arenes by Ammonia and Primary Amines[1]

Summary: Direct photoamination of arenes efficiently occurs with ammonia and various primary amines in the presence of *m*-dicyanobenzene to give aminated dihydroarenes in fairly good yields.

Sir: The preparation of aromatic amines is usually carried out by means of indirect methods involving reductions of nitro, azo, and azide arenes or substitution of the halogen, hydroxy, and alkoxy groups.[2,3] On the other hand, direct amination of arenes is limited to Fridel–Crafts reaction with activated amination reagents or nucleophilic addition of amide anion to highly activated substrates.[2] From

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(2) Gibson, M. S. In "The Chemistry of the Amino Group"; Patai, S., Ed.; Interscience: New York, 1968; pp 37–77.

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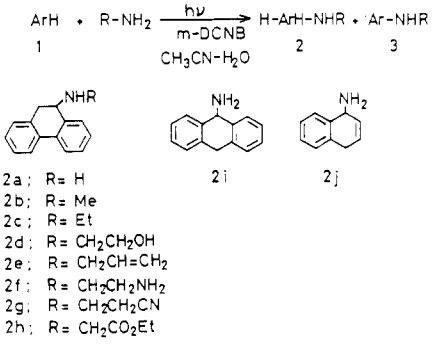
Table I. Photoamination of Arenes[a]

run	arene (1)	RNH_2	irradn time, h	products (yield, %)[b]	conversion of ArH, %	recovery of *m*-DCNB, %
1	phenanthrene (**1a**)	NH_3	17	**2a** (84)	88	97
2[c]		NH_3	17	**2a** (0)	25	
3[d]		NH_3	17	**2a** (64)	74	100
4		$MeNH_2$	12	**2b** (82)	74	92
5		$EtNH_2$	12	**2c** (95)	76	83
6[c]		$EtNH_2$	12	**2c** (0)	10	
7		$HOCH_2CH_2NH_2$	24	**2d** (82)	76	40
8		$CH_2{=}CHCH_2NH_2$	12	**2e** (85)	79	35
9		$H_2NCH_2CH_2NH_2$	15	**2f** (95)	58	67
10		$NCCH_2CH_2NH_2$	14	**2g** (66)	71	57
11		$EtOCOCH_2NH_2$	16	**2h** (78)	59	94
12	anthracene (**1b**)	NH_3	18	**2i** (88)	82[e]	100
13	naphthalene (**1c**)	NH_3	20	**2j** (48), **3a** (13)	97	100

[a] Into 140 mL of a 10% aquous acetonitrile solution containing 1 (14 mmol) and *m*-DCNB (3.5 mmol) was dissolved ammonia or an amine (140–350 mmol). In run 12, smaller amounts of **1b** (3 mmol) and *m*-DCNB (1.5 mmol) were used because of low solubility of **1b**. The solutions were irradiated with a high-pressure mercury lamp, then evaporated under reduced pressure, and dissolved into 150 mL of benzene. Extraction with dilute HCl followed by basification with saturated $NaHCO_3$ gave the aminated products. The starting arenes and *m*-DCNB were recovered from benzene solutions. [b] Isolated yields based on consumed 1. [c] In the absence of *m*-DCNB. [d] Dry acetonitrile solutions. [e] Anthracene was recovered as photodimer.

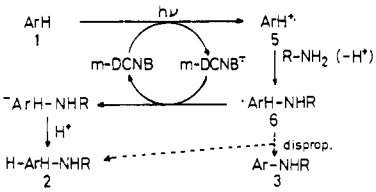
synthetic points of view, it is requisite to find a general method for direct amination of aromatic nuclei using ammonia and unactivated amines as amination reagents. As parts of our investigation on synthetic applications of photochemical electron transfer,[4,5] we attempted to explore possiblities of the nucleophilic addition of ammonia and amines to the photogenerated cation radical of arenes. In this paper, we wish to report efficient, direct photoamination of arenes by ammonia and primary amines in the presence of *m*-dicyanobenzene (*m*-DCNB). It is of synthetic significance to note that the present photoamination is applicable to direct introduction of various bifunctional amines.

A 9:1 (v/v) acetonitrile–water solution containing an arene **1a–c**, *m*-DCNB, and ammonia or a primary amine was irradiated through Pyrex by a high-pressure mercury arc under argon at room temperature; dihydroaminoarenes **2a–j** were selectively formed in fairly good yield, whereas



m-DCNB was mostly recovered except for a few cases (Table I). It should be noted that the photoamination of **1a** with bifunctional alkyl amines containing the hydroxy, amino, cyano, ethoxycarbonyl, and vinyl groups selectively occurs without reactions of the other functional groups. It was confirmed that no reaction occurs in the dark as well as in the absence of *m*-DCNB. The structures of **2a–j** and **3a** were obtained from IR, NMR, and mass spectra as well as from elemental analyses of the acetamide or benzamide derivatives (supplementary material).

Scheme I



As has been discussed earlier,[4,5] electron transfer from the excited-singlet arenes to *m*-DCNB is certainly responsible for the primary process of these reactions, since the fluorescence of the arenes was quenched by *m*-DCNB at a diffusion-controlled limit in 9:1 acetonitrile–water, while no fluorescence quenching occurred with ammonia and the amines. The aromatic cation radicals **5** thus formed are nucleophilically attacked by ammonia and the primary amines to give adduct radicals **6**. The final products **2** are thus formed mainly by one-electron reduction of **6** with *m*-DCNB$^{-}\cdot$ as is shown in Scheme I. The participation of disproportionation of **6** should be taken into account in the photoamination of **1c** since a significant amount of **3a** was formed. In the other cases, however, the lack of formation of **3** indicates negligible disproportionation of **6** in the formation of **2**.

It is of synthetic interest to note that ethanolamine and allylamine selectively react at the amino group as a consequence perhaps originating from the much higher nucleophilicity toward **5** compared with the hydroxy or olefinic group. Preliminary experiments demonstrated wide applicabilities of the present method to amination of a variety of arenes such as methylnaphthalenes, methoxynaphthalenes, biphenyl, and dimethoxybenzenes.[6] Although the photoamination with such secondary amines as dimethylamine was attempted,[7] it was found that the photoreactions proceed very inefficiently along with substantial consumption of *m*-DCNB.

We are now intending to attempt further applications of the photoamination as well as chemical transformation **2d–h** to azacyclic compounds.[8]

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(6) The results will be published in a full paper.

(7) The photoreactions of anthracene or naphthalene with dialkylamines in the absence of *m*-DCNB were reported to give the dialkyl derivatives of **2i** or **2j** as a major product, respectively, see: Yang, N. C.; Libman, J. *J. Am. Chem. Soc.* **1973**, *95*, 5783–5784. Barltrop, J. A. *Pure Appl. Chem.* **1973**, *33*, 179.

(8) For example, **2d** can be easily converted to *N*-(9,10-dihydro-9-phenanthryl)aziridine by usual procedures.

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Registry No. **1a**, 85-01-8; **1b**, 120-12-7; **1c**, 91-20-3; **2a**, 97825-83-7; **2b**, 97825-84-8; **2c**, 97825-85-9; **2d**, 97825-86-0; **2e**, 97825-87-1; **2f**, 97825-88-2; **2g**, 97825-89-3; **2h**, 97825-90-6; **2i**, 97825-91-7; **2j**, 97825-92-8; **3a**, 134-32-7; NH_3, 7664-41-7; $MeNH_2$, 74-89-5; $EtNH_2$, 75-04-7; $HO(CH_2)_2NH_2$, 141-43-5; $CH_2{=}CHCH_2NH_2$, 107-11-9; $NH_2(CH_2)_2NH_2$, 107-15-3; $NC(CH_2)_2NH_2$, 151-18-8; $EtOC(O)CH_2NH_2$, 459-73-4.

Supplementary Material Available: A table of melting points and ^1H NMR spectral and elemental analyses data for compounds **2a–j** (2 pages). Ordering information is given on any current masthead page.

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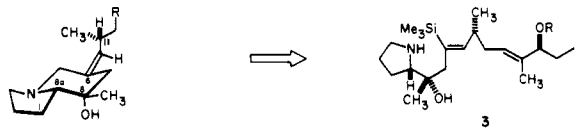
Enantioselective Total Synthesis of (+)-Pumiliotoxin A

Summary: (+)-Pumiliotoxin A (**2**), the parent alkaloid of the cardiac-active pumiliotoxin A class, can be prepared in 13 steps and 5% overall yield from (*S*)-(−)-2-methyl-1-penten-3-ol (**4**). This enantioselective total synthesis establishes, for the first time, the complete stereostructure of **2**.

Sir: Daly and co-workers[1] first isolated pumiliotoxins A (**2**) and B (**1**) from the Panamanian poison frog *Dendrobates pumilio* in 1967.[1,2] The structure of the powerful



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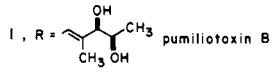
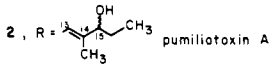


1, R = pumiliotoxin B

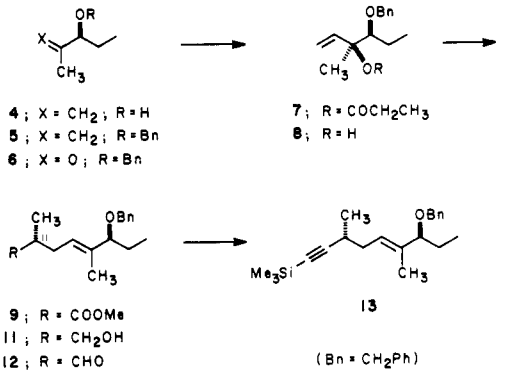


2, R = pumiliotoxin A

cardiotonic agent[1,3] pumiliotoxin B (**1**) has now been rigorously established by a combination of spectroscopic,[4] degradative,[5] and total synthesis[6] studies. In contrast, the stereostructure of pumiliotoxin A,[4,7] the parent alkaloid of the pumiliotoxin A class,[2] is not known. Recent studies[7] indicate that samples of **2** isolated from *Dendrobates pumilio* are mixtures of two isomers that are surmised to be epimers at C-15. In this paper, we report the synthesis of (+)-pumiliotoxin A (**2**) from (*S*)-(−)-2-methyl-1-penten-3-ol (**4**).[8] This enantioselective total synthesis rigorously establishes the complete stereostructure of **2** and demonstrates that the major isomer of (+)-pumiliotoxin A isolated from dendrobatid frogs has the *S* configuration at C-15 (**2**, β-OH). Moreover, the convergent synthesis strategy described herein achieves by far the most efficient entry to the biologically important[2] pumiliotoxin A alkaloids to be developed to date.

The chemical objective of this total synthesis endeavor was to examine whether the iminium ion–vinylsilane cyclization approach[6] for constructing the (*Z*)-6-alkylideneindolizidine ring system of this cardiac toxin class would succeed with a fully functionalized side chain, i.e. **3** → **2**. This strategy is attractive since it is much more convergent than the approach we had previously employed[6] to prepare (+)-pumiliotoxin B.

A key intermediate in the experimental verification of this approach is (−)-silylalkyne **13**, which embodies the fully elaborated side chain of pumiliotoxin A. The synthesis of **13** starts with the *S* alcohol **4**[8] ($[\alpha]^{25}_D$ −4.9° (*c* 0.63, $CHCl_3$); >98% ee[9]), which is readily obtained by Sharpless kinetic resolution.[10] Benzylation of **4** (NaH, BnBr; 86%



4; X = CH_2; R = H
5; X = CH_2; R = Bn
6; X = O; R = Bn

7; R = $COCH_2CH_3$
8; R = H

9; R = COOMe
11; R = CH_2OH
12; R = CHO

13

(Bn = CH_2Ph)

yield) provides **5**,[11] which is successfully cleaved with 1 equiv[12] of O_3 (−78 °C, MeOH; Me_2S; 84% yield) to give α-benzyloxy ketone **6**[11] ($[\alpha]^{25}_D$ −113° (*c* 2.6, $CHCl_3$)). The reaction of **6** with vinylmagnesium bromide (THF, 25 °C) occurs with >99% stereoselectivity[13] to afford the syn

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(3) See, inter alia: Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. *J. Med. Chem.* **1985**, *28*, 482. Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Kauffman, F. C.; Tamburni, R.; Nimit, Y.; Daly, J. W. *Mol. Pharmacol.* **1981**, *19*, 411.
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(7) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron*, **1984**, *40*, 1183.
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(10) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
(11) Isolated intermediates showed correct molecular compositions (elemental analysis or high-resolution MS) and appropriate NMR and mass spectra.
(12) Careful monitoring by TLC is necessary to avoid overoxidation to give unwanted benzoate.
(13) See, inter alia: Still, W. C.; McDonald, J. H., III. Tetrahedron Lett., **1980**, 1031.

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