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Rhodium-Catalyzed Addition of Arylboronic Acids to Alkynyl Aza-Heteroaromatic Compounds in Water

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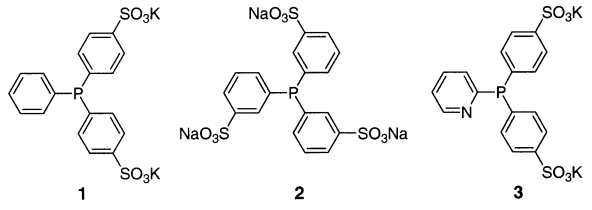
Alkynyl heteroaromatic compounds reacted with arylboronic acids to give addition products in the presence of a rhodium catalyst. The best results were obtained when a novel pyridine-substituted water-soluble phosphine ligand was used. The reactions proceed to give trisubstituted alkenes from various arylboronic acids and alkynyl heteroaromatic compounds with high regioselectivity. Only alkynes with a nitrogen atom in proximity to the triple bond were converted to the corresponding alkenes, as expected for a chelation-controlled addition.

Introduction

Organic reactions in aqueous medium have received significant attention as a result of environmental and economic considerations. The formation of carbon−carbon bonds using a transition-metal catalyst in water represents one of the most attractive strategies in this area.[1] Because normal transition-metal catalysts generally have low solubility and low reactivity in water, various water-soluble ligands have been developed to solve these problems.[2] TPPDS (**1**) and TPPTS (**2**) are the most



popular water-soluble ligands,[3] which are utilized in a variety of transition metal-catalyzed reactions.[4−6]

Rhodium-catalyzed reactions of boronic acids to activated alkenes in aqueous media have emerged as a highly efficient methods for the formation of carbon−carbon bonds. Hayashi and Miyaura reported the asymmetric 1,4-addition of organoboronic acids to various α,β-unsaturated compounds (Scheme 1).[7] In these reactions, only olefins activated by the presence of a conjugated

(1) For reviews of organic synthesis in water, see: (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, 1998. (b) Li, C. J.; Chan, T. H. *Organic Reactions in Organic Media*; John Wiley and Sons: New York, 1997. (c) Cornils, B.; Herrmann, W. A. *Aqueous Phase Organometallic Chemistry: Concepts and Applications*; Wiley-VCH: Weinheim, 1998. (d) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (e) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (f) Li, C. J. *Tetrahedron* **1996**, *52*, 5643.

(2) For review of water-soluble ligands, see: (a) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. (b) Joó, F.; Kathó, Á. *J. Mol. Catal. A* **1997**, *116*, 3. (c) Katti, K. V.; Gali, H.; Smith, C. J.; Berning, D. E. *Acc. Chem. Res.* **1999**, *32*, 9. (d) Genet, J. P.; Saignac, M. *J. Organomet. Chem.* **1999**, *576*, 305. (e) Genet, J. P.; Saignac, M.; Lemaire-Audoire, S. In *Transition Metal Catalysed Reactions*; Murahashi, S.; Davies, S. G., Eds.; Blackwell Science: Oxford, 1999; p 55.

(3) These ligands are commercially available from Strem Chemicals.

(4) For recent representative reactions using TPPTS: (a) Mignani, G.; Morel, D.; Colleuille, Y. *Tetrahedron Lett.* **1985**, *26*, 6337. (b) Mignani, G.; Morel, D.; Colleuille, Y. *Tetrahedron Lett.* **1986**, *27*, 2591. (c) Grosselin, J. M.; Mercier, C.; Allmang, G.; Grass, F. *Organometallics* **1991**, *10*, 2126. (d) Genet, J. P.; Linquist, A.; Blard, E.; Mouries, V.; Savignac, M.; Vaultier, M. *Tetrahedron Lett.* **1995**, *36*, 1443. (e) Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829. (f) Galland, J.-C.; Savignac, M.; Genet, J.-P. *Tetrahedron Lett.* **1997**, *38*, 8695. (g) Galland, J.-C.; Savignac, M.; Genet, J.-P. *Tetrahedron Lett.* **1999**, *40*, 2323. (h) Bhanage, B. M.; Ikushima, Y.; Shirai, M.; Arai, M. *Tetrahedron Lett.* **1999**, *40*, 6427. (i) Djoman, M. C. K.-B.; Ajjou, A. N. *Tetrahedron Lett.* **2000**, *41*, 4845. (j) Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genet, J.-P. *Org. Lett.* **2001**, *3*, 2065. (k) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523. (l) Francisco, L. W.; Moreno, D. A.; Atwood, J. D. *Organometallics* **2001**, *20*, 4237.

(5) For reactions using TPPDS, see: (a) Thorpe, T.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2000**, *41*, 4503. (b) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358. (c) Chen, H.; Li, Y.; Chen, J.; Cheng, P.; Li, X. *Catal. Today* **2002**, *74*, 131.

(6) For representative other examples of transition metal chemistry of water-soluble phosphine, see: (a) Smith, R. T.; Ungar, R. K.; Sanderson, L. J.; Baird, M. C. *Organometallics* **1983**, *2*, 1138. (b) Darensbourg, D. J.; Joo, F.; Kannisto, M.; Katho, A.; Reibenspies, J. H. *Organometallics* **1992**, *11*, 1990. (c) Tóth, I.; Hanson, B. E. *Organometallics* **1993**, *12*, 1506. (d) Jones, A.; Roberts, D. L.; Davis, M. E. *Nature* **1994**, *370*, 449. (e) Ding, H.; Hanson, B. E.; Bakos, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1645. (f) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317. (g) Shin, S.; RajanBabu, T. V. *Org. Lett.* **1999**, *1*, 1229. (h) Yonehara, K.; Hashizume, T.; Mori, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 5593. (i) Kovacs, J.; Todd, T. D.; Reibenspies, J. H.; Joo, F.; Darensbourg, D. J. *Organometallics* **2000**, *19*, 3963. (j) Ueda, M.; Nishimura, M.; Miyaura, N. *Synlett*, 856. (k) Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757. (l) Lucey, D. M.; Atwood, J. D. *Organometallics* **2002**, *21*, 2105. (m) Raghuraman, K.; Pillarsetty, N.; Volkert, W. A.; Barnes, C.; Jurisson, S.; Katti, K. V. *J. Am. Chem. Soc.* **2002**, *124*, 7276.

(7) For additions to enones, see: (a) Sakai, M.; Hayashi, M.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. For additions to α,β-unsaturated esters, see: (c) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. For additions to vinyl phosphonates, see: (d) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. For additions to vinyl nitro compounds, see: (e) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

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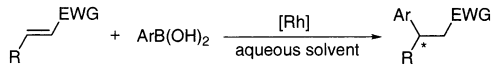
SCHEME 1



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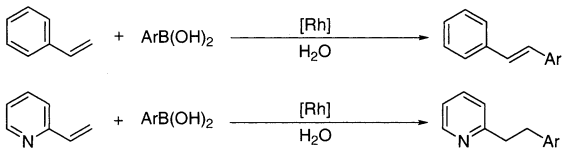

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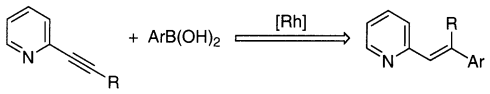
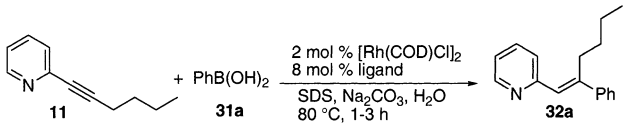


electron-withdrawing group could be used, and the reactions generally must be carried out in an organic solvent−water mixture. Recently, we reported the rhodium-catalyzed reactions of various arylboronic acids to alkenes (Scheme 2).[5b] The reactions could be applied to unactivated olefins such as aromatic or heteroaromatic olefins in neat water by using TPPDS (**1**), and it was clear that the reaction outcome changes completely depending on the type of olefin. When styryl olefins were used, 1,2-diarylethylenes were produced, which arose from a "Heck-type" addition−β-H elimination process.[8] When heteroaromatic olefins were used, the addition products arising from an addition−hydrolysis pathway were obtained. We sought to determine whether rhodium catalysts could promote the addition of boronic acids to other unsaturated compounds such as alkynes (Scheme 3).[9,10] We thought that regioselective addition occurs with alkynyl heteroaromatic compounds to give trisubstituted alkenes. Furthermore, it was clear that the water-soluble ligand **3**, which has a pyridyl phosphine moiety, shows high reactivity in the reaction. We now present a full description of our results.

Results and Discussion

Alkynyl heteroaromatic compounds for rhodium-catalyzed addition were synthesized as follows (Scheme 4). Alkynes having various heteroaromatics **11**−**16** were synthesized by Sonogashira coupling[11] of aryl bromides **4**−**9** with 1-hexyne **10** in 59−92% yield. Similarly, substrates with various substituent on the alkyl side chain (**22**−**26**) could be made from 2-bromopyridine **4** and alkynes **17**−**21** in 90−98% yield. Alkyne **24**, which has a 3-hydroxypropyl group, was converted to a silylated compound **27** in 87% yield. From the reactions of 2,6- (**28**) and 2,5-dibromopyridine (**9**) with 1-hexyne, dialkynes **29** and **30** in which two alkynyl groups are present on the pyridine ring were obtained in 91% and 97% yield.

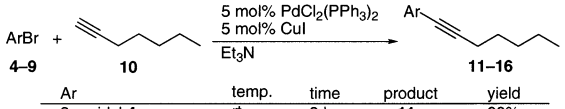
TABLE 1



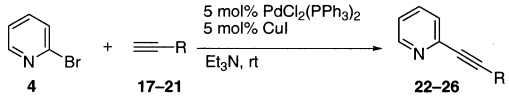
entry	ligand	yield (%)	entry	ligand	yield (%)
1	TPPDS (**1**)	25 (35)[a]	4	dppe	<10[c]
2	TPPTS (**2**)	NR[b]	5	dppe	NR[d]
3	PPh_3	<10[c]	6	**3**	51

[a] The yield in parentheses is based on recovered starting material. [b] No reaction. [c] Considerable amount of starting material remained. [d] The reaction was caried out in the absence of SDS in dioxane/H_2O = 10/1.

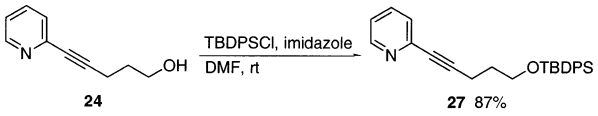
SCHEME 4

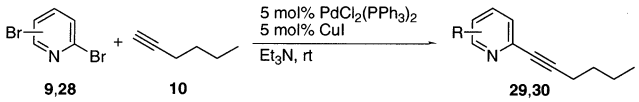


Ar	temp.	time	product	yield
2-pyridyl **4**	rt	3 h	**11**	98%
3-pyridyl **5**	50°C	2 days	**12**	68%
4-pyridyl **6**	rt	5 h	**13**	80%
2-pyrimidyl **7**	rt	5 h	**14**	59%
2-quinolyl **8**	rt	3 h	**15**	83%
5-bromo-2-pyridyl **9**	rt	1 h	**16**	92%



R	time	product	yield
benzyl **17**	5 h	**22**	91%
phenyl **18**	3 h	**23**	98%
3-hydroxypropyl **19**	3 h	**24**	91%
2-hydroxyethyl **20**	3 h	**25**	90%
hydroxymethyl **21**	3 h	**26**	92%





Br	temp.	time	product	yield
6-bromo **28**	rt	5 h	R = 6-(1-hexynyl) **29**	91%
5-bromo **9**	50°C	3days	R = 5-(1-hexynyl) **30**	97%

Our intitial attempt at rhodium-catalyzed addition began with 2-(1-hexynyl)pyridine **11** and phenylboronic acid **31a**. (Table 1). According to our standard protocol for addition to alkenes,[5b] the reaction of **11** with **31a** in the presence of 2 mol % $[Rh(COD)Cl]_2$, 8 mol % TPPDS (**1**), Na_2CO_3, and sodium dodecyl sulfate (SDS) in water at 80 °C for 3 h gave the corresponding addition product **32a** in 25% yield (35% yield based on recovered starting material) (Table 1, entry 1). The reaction using TPPTS (**2**) failed completely (entry 2), and organic-soluble phosphine ligands such as PPh_3 and dppe led to low conversion (entries 3 and 4). No reaction was observed in 10/1 dioxane/H_2O solvent, in analogy with the conditions reported by Hayashi and Miyaura[7] (entry 5). Our attention turned to finding a new catalyst system that would promote the addition. Recently, we determined that the

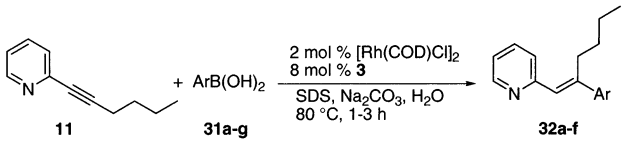
(8) Recently, Brown reported ruthenium-catalyzed oxidative Heck reactions of arylboronic acids to activated alkenes: Farrington, E. J.; Brown, J. M.; Barnard, C. F. J.; Rowsell, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 169.

(9) For a previous communication, see: Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123.

(10) Recently, Hayashi reported a similar type addition to alkynes: Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918.

(11) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 521.

TABLE 2.



entry	boronic acid	product	yield (%)
1	phenyl **31a**	**32a**	51
2	2-methylphenyl **31b**	**32b**	81
3	2,6-dimethylpenyl **31c**	**32c**	86
4	1-naphthyl **31d**	**32d**	72
5	4-methoxyphenyl **31e**	**32e**	57[a]
6	2-methyl-4-methoxyphenyl **31f**	**32f**	83[a]
7	4-acetyl **31g**		dec

[a] 4 mol % $[Rh(COD)Cl]_2$, 16 mol % **3** and 5 equiv of boronic acid were used.

rhodium-catalyzed reaction of arylboronic acids to alkenes effectively proceeds in the presence of pyridine.[12] Additives including pyridine were found to influence the ratio of Heck-type products to addition products in some substrates. For example, while the reaction of 1-nitro-4-vinylbenzene with 2-methylpheylboronic acid under standard conditions gave a mixture of addition−β-H elimination and addition−hydrolysis, the addition of pyridine to the reaction mixture led to the generation of addition−hydrolysis product exclusively in high yield. On the basis of this result, we planned to use a novel water-soluble ligand **3**, which has a pyridyl phosphine moiety within the molecule. Phosphine **3** was first synthesized by Stelzer in 1993,[13] but there are no reports of using this compound as a ligand in catalysis. We were very pleased to find that the reaction proceeded smoothly to afford **32a** in 51% yield when **3** was used (entry 6).

A series of substituted arylboronic acids **31a**−**g** were then subjected to the reaction conditions to further define the reaction scope (Table 2). Substitution at the ortho position of the arylboronic acid gave better results (entries 2−4), and the yield increased to 86% when 2,6-dimethylphenylboronic acid **31c** was used (entry 3). Although the catalyst loading must be increased (4 mol % $[Rh(COD)Cl]_2$, 16 mol % **3**), the corresponding products **32e** and **32f** were obtained in good yield with arylboronic acids **31e** and **31f** bearing a methoxyl group (entries 7 and 8). Acetylphenylboronic acid **31g** was ineffective for the addition to the alkyne (entry 8). Adducts **32a**−**f** were isolated as the sole products, and it was clear by ^{1}H NMR that the reactions proceed with high regioselectivity. The geometry of the addition product **32e** was determined by ROESY, and the other adducts were assumed to the same (Figure 1).

The results of the rhodium-catalyzed reactions of alkynes containing various heteroaromatics **11**−**16** and **33** in the presence of ligand **3** are summarized in Table 3. In contrast to the reaction of **11** (entry 1), the reactions of **12** and **13**, which have the alkynyl group at the meta and para positions on the pyridine ring, failed to undergo the addition (entries 2 and 3). The desired product **34** was produced in low yield, and polymerized products

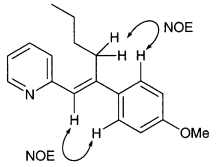


FIGURE 1. ROSEY correlation of **32e**.

TABLE 3. Reactions Using Various Heteroaromatic-Containing Alkynes[a]

entry	substrate	product[b]	yield (%)
1	**11** R = 2-(1-hexynyl)	**32b**	81
2	**12** R = 3-(1-hexynyl)		N.R.
3	**13** R = 4-(1-hexynyl)		N.R.
4	**33**	**34**	<15[c]
5	**14**	**35**	69[d]
6	**15**	**36**	63
7	**16**	**37**	66[e]

[a] Reactions were carried out in the presence of 2 mol % $[Rh(COD)Cl]_2$, 8 mol % **3**, 2.5 equiv of 2-methylphenylboronic acid, SDS, and Na_2CO_3 in H_2O at 80 °C for 1−3 h. [b] Ar = 2-methylphenyl (entries 1, 5−7), Ar = phenyl (entry 4). [c] 2.5 equiv of phenylboronic acid was used. [d] The reaction was carried out at 60 °C.[e] 4 mol % $[Rh(COD)Cl]_2$, 16 mol % **3**, and 5 equiv of 2-methylphenylboronic acid **5b** were used.

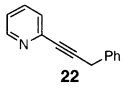
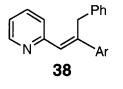
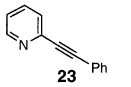
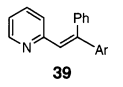
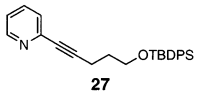
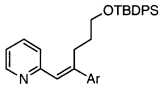
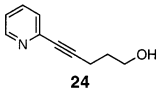
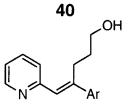
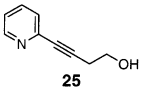
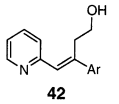
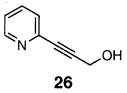
were mainly obtained when 1-phenylpropyne **33** was subjected to the reaction conditions (entry 4). From these results, it is expected that the nitrogen atom in the aromatic ring is necessary and must be located adjacent to the triple bond to promote the addition. When alkynes **14** and **15** bearing pyrimidyl and quinolyl group were subjected to the reaction, the corresponding products **35** and **36** were obtained in good yields (entries **5** and **6**). The bromoarylalkyne **16** reacted to afford **37** in 66% yield, demonstrating chemoselectivity (entry **7**).

The reactions of pyridylalkynes having various substituents on the alkyne were also examined (Table 4). A benzyl group (**22**) underwent reaction to give **38** in 66% yield (entry 1). In contrast, the phenyl-substituted alkyne **23** reacted sluggishly (entry 2), perhaps because of steric hindrance caused by the phenyl group. A substrate containing a siloxyl group within the alkyl side chain (**27**) was successfully transformed to **40** in 83% yield (entry 3). Furthermore, alkynes with a free hydroxyl group such as **24** and **25** were also converted to **41** and **42** in moderate yields (entries 4 and 5); however, a substrate containing a hydroxyl group at the propargyl position (**26**) failed to react (entry 6).

We next tried the reaction of **27** and **28**, in which two alkynyl groups were present on the pyridine ring (Scheme 5). When **27** was treated with 5 equiv of 2-methylphenylboronic acid **31b** in the presence of 4 mol % [Rh(COD)-

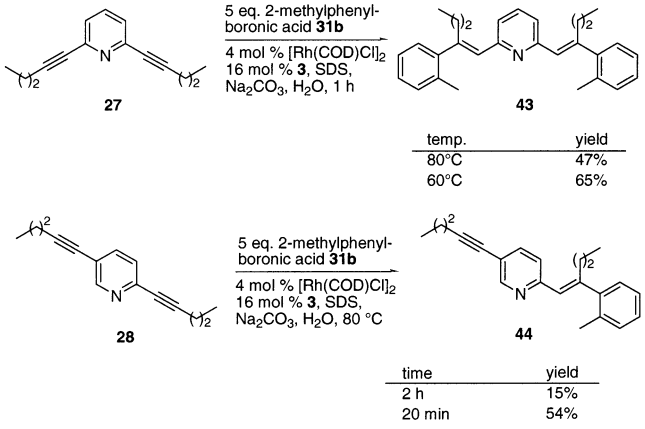
(12) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B.; Yoshida, M. Manuscript in preparation.
(13) Herd, O.; Langhans, P. K.; Stelzer, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1058.

TABLE 4. Reactions Using Various Substituted Pyridylalkynes[a]

entry	substrate	product[b]	yield (%)
1	 **22**	 **38**	66[c]
2	 **23**	 **39**	trace[d]
3	 **27**	 **40**	83
4	 **24**	 **41**	79
5	 **25**	 **42**	60
6	 **26**	–	N.R.

[a] Reactions were carried out in the presence of 2 mol % $[Rh(COD)Cl]_2$, 8 mol % **3**, 2.5 equiv of 2-methylphenylboronic acid, SDS, and Na_2CO_3 in H_2O at 80 °C for 1−3 h. [b] Ar = 2-methylphenyl. [c] 4 mol % $[Rh(COD)Cl]_2$, 16 mol % **3**, and 5 equiv of 2-methylphenylboronic acid **5b** were used. [d] A considerable amount of starting material remained.

SCHEME 5



$Cl]_2$ and 8 mol % **3** at 80 °C, the double addition product **43** was produced in 47% yield. The yield was increased to 65% by conducting the reaction at 60 °C. Interestingly, substrate **28**, which has an alkynyl group at both an ortho and meta position, was selectively converted into the monoadduct **44** after 20 min, demonstrating that it was possible to distinguish two alkynes within a single molecule. The yield was dramatically decreased when the reaction was carried out for 2 h (54 vs 15% yield), implying that the alkynyl group at the meta position eventually reacts but leads to complex mixtures.

A plausible mechanism for the reaction is shown in Figure 2. It is presumed that (hydroxo)rhodium(I) complex **45** exits as an active species in this reaction,[14] and a catalytic cycle would involve the transmetalation of the

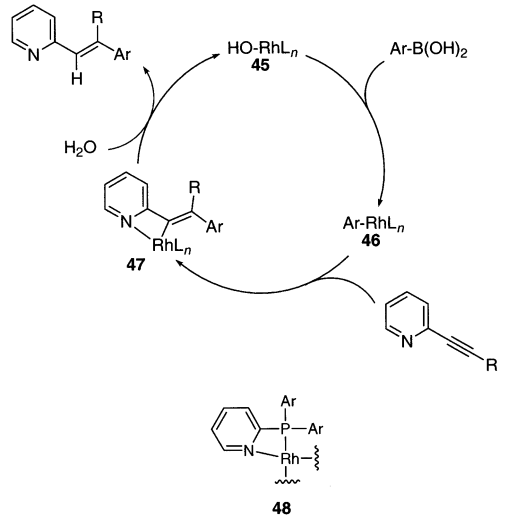
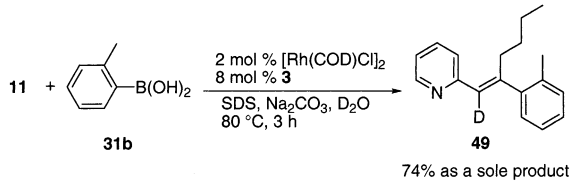


FIGURE 2.

SCHEME 6



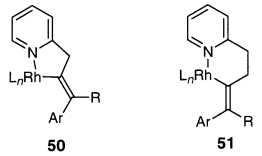
arylboronic acid to the rhodium species **45** to give the arylrhodium complex **46** as the initial step. Next, the coordination of the alkynyl and pyridyl group of the substrate to rhodium followed by regioselective insertion into the Rh−C bond would give the alkenylrhodium complex **47**. The observation that only alkynes substituted at the ortho position on the pyridine ring reacted with arylboronic acids supports a chelation-controlled insertion process.[15] Finally the hydrolysis of the complex **47** with water would afford the product and the regenerated rhodium species **45**.

The cause of the increased reactivity of the pyridine-base ligand is not clear, but it might also be related to chelation. Simultaneous coordination of the phosphine and the nitrogen to rhodium as shown in **48** is possible.

Information on the reaction mechanism was gained when the reaction of **11** with **31b** was run in D_2O (Scheme 6). In this case, deuterium was incorporated quantitatively at the alkenyl position to give **49** in 74% yield. Recently, Hayashi has also reported the rhodium-catalyzed addition of arylboronic acids to alkynes.[10]

(14) (a) Brune, H.-A.; Unsin, J.; Hemmer, R.; Reichhardt, M. *J. Organomet. Chem.* **1989**, *369*, 335. (b) Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126. (c) Grushin, V. V.; Kuznetsov, V. F.; Bensimon, C.; Alper, H. *Organometallics* **1995**, *14*, 3927, and see also ref 4c. (d) Hayashi, T.; Takahasi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

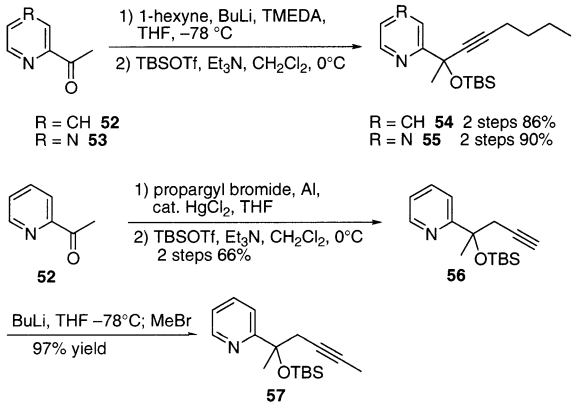
(15) For examples of the chelation-controlled rhodium-catalyzed reactions, see: (a) Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 12043. (b) Jun, C.-H.; Lee, H.; Moon, C. H.; Hong, H.-S. *J. Am. Chem. Soc.* **2001**, *123*, 8600. (c) Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751. (d) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (e) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880. (f) Jun, C.-H.; Lee, D.-Y.; Hong, J.-B. *Tetrahedron Lett.* **1997**, *38*, 6673. (g) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200.



50 **51**

FIGURE 3.

SCHEME 7



In this work, a 1,4-shift of rhodium from the vinylic position to the ortho position of the phenyl group was proposed to explain the labeling studies, but we did not observe this 1,4-shift under our reaction conditions. It is expected that the relatively stable chelated alkenylrhodium complex **47** would prevent the 1,4-shift of rhodium.

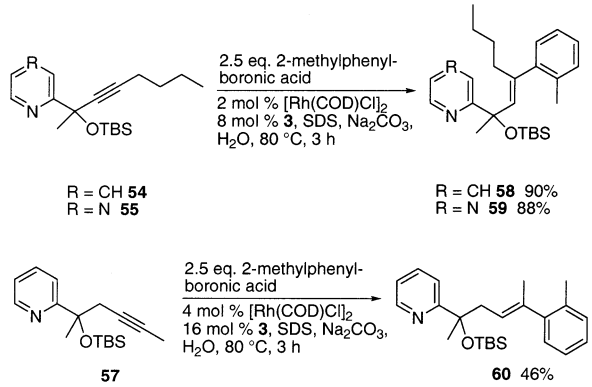
To confirm the proposal of a chelation-controlled regioselective addition mechanism, we next examined the reactions using alkynes having a triple bond one and two carbons away from the pyridyl group. These substrates would form chelated five- and six-membered ring intermediates **50** and **51** to give the corresponding adducts with high regioselectivity (Figure 3).

Syntheses of the substrates were performed as shown in Scheme 7. 2-Acetylpyridine **52** was subjected to the addition of 1-hexyne **10** in the presence of *n*-BuLi, followed by the protection of the yielded tertiary alcohol with the TBS group to give pyridine-ring-containing **54** in two steps in 86% yield. Pyrazine-ring-containing substrate **55** was also prepared from **53** in two steps in 90% yield. Alkyne **57** could be made from **52** in three steps via addition of the propargyl unit in the presence of aluminum,[16] followed by silylation of alcohol and methylation of the terminal alkyne.

When the reaction of **54** with 2-methylphenylboronic acid was carried out, the desired adduct **58** was produced in 90% yield as the sole product (Scheme 8). Similarly, **59** was obtained in 88% yield from **55**. Although the product yield decreased to 47%, the reaction using **57** was successful, giving **60** predominantly. These results provide good evidence that the chelation-controlled regioselective addition is operating. The low conversion of **57** may be due to formation of a six-membered ring chelation (**51**), compared to four- and five-membered ring complexes.

(16) Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 81, and references therein.

SCHEME 8



Conclusion

In conclusion, we have developed a rhodium-catalyzed addition of arylboronic acids to alkynes. The reactions can be run in neat water, and it was found that the reaction is best carried out in the presence of the novel pyridine-substituted ligand **3**. The reactions enable the construction of trisubstituted olefins with high regioselectivity using heteroaromatic contained alkynes. A variety of alkynes can be chemoselectively converted to the corresponding addition products. It is expected that the addition would proceed by chelation to the nitrogen moiety, and two alkynes at different positions on the pyridine ring could be distinguished. The reactions also applied to the alkynes one and two carbons away from the pyridyl group. Application of this catalyst system to other types of reactions are now in progress.

Experimental Section

The following includes general experimental procedures and spectroscopic information for all illustrative new compounds. The spectral data of **11**,[17] **23**,[18] **26**,[19] and **34**[20] are in complete agreement with the literature's data. Materials were obtained from commercial suppliers and used without further purification. Solvents were dried and distilled according to standard protocols. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure.

General Procedures for the Preparation of Substrates. To a stirred suspension of 2-bromopyridine (500 mL, 3.17 mmol), $PdCl_2(PPh_3)_2$ (111.2 mg, 0.158 mmol), and CuI (0.158 mL, 30.2 mmol) in Et_3N (20 mL) was added dropwise 2-hexyne (0.436 mL, 3.79 mmol) at room temperature, and stirring was continued for 3 h at the same temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was purified by chromatography on silica gel with hexanes:Et_2O (75:25 v/v) as eluent to give **11** (497 mg, 98%) as a colorless oil.

3-(1-Hexynyl)pyridine (12): R_f = 0.44 (50% Et_2O in hexane); IR (neat) 2958, 2933, 2872, 2232, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (1H, s), 8.47 (1H, d, J = 4.8 Hz), 7.66 (1H, d, J = 7.8 Hz), 7.20 (1H, dd, J = 7.8, 4.8 Hz), 2.43

(17) Sato, N.; Hayakawa, A.; Takeuchi, R. *J. Heteroycl. Chem.* **1990**, *27*, 503.

(18) Okubo, J.; Shinozuka, H.; Koitabashi, T.; Yomura, R. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 329.

(19) Al-Arnaout, A.; Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1987**, *333*, 139.

(20) Kawashima, T.; Ishii, T.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1831.

(2H, t, J = 7.2 Hz), 1.65−1.54 (2H, m), 1.54−1.42 (2H, m), 0.95 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 147.8, 138.3, 122.8, 121.1, 94.0, 77.2, 30.5, 21.9, 19.0, 13.5; MS m/z 159 (M^+); HRMS m/z calcd for $C_{11}H_{13}N$ 159.1048 (M^+), found 159.1039.

4-(1-Hexynyl)pyridine (13): R_f = 0.36 (50% Et_2O in hexane); IR (neat) 2958, 2933, 2872, 2234, 1594, 1538 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (2H, d, J = 6.0 Hz), 7.21 (2H, d, J = 6.0 Hz), 2.42 (2H, t, J = 6.9 Hz), 1.64−1.53 (2H, m), 1.53−1.41 (2H, m), 0.95 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 132.2, 125.6, 95.9, 78.3, 30.4, 22.0, 19.2, 13.6; MS m/z 159 (M^+); HRMS m/z calcd for $C_{11}H_{13}N$ 159.1048 (M^+), found 159.1051.

2-(1-Hexynyl)-1,3-pyrimidine (14): R_f = 0.42 (50% Et_2O in hexane); IR (neat) 2959, 2855, 2234, 1564, 1553 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (2H, d, J = 5.1 Hz), 7.22 (1H, d, J = 5.1 Hz), 2.48 (2H, t, J = 7.2 Hz), 1.70−1.66 (2H, m), 1.56−1.44 (2H, m), 0.94 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 153.1, 119.3, 90.8, 79.8, 29.9, 21.9, 18.8, 13.4; MS m/z 160 (M^+); HRMS m/z calcd for $C_{10}H_{12}N_2$ 160.1000 (M^+), found 160.0993.

2-(1-Hexynyl)quinoline (15): R_f = 0.24 (10% Et_2O in hexane); IR (neat) 2957, 2856, 2226, 1616, 1594, 1553, 1500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, d, J = 3.6 Hz), 8.02 (1H, d, J = 3.6 Hz), 7.73−7.65 (2H, m), 7.49−7.42 (2H, m), 2.49 (2H, t, J = 7.2 Hz), 1.69−1.62 (2H, m), 1.55−1.46 (2H, m), 0.95 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 144.0, 135.8, 129.6, 129.0, 127.2, 126.7, 126.5, 124.0, 91.9, 81.0, 30.2, 22.0, 19.0, 13.5; MS m/z 209 (M^+); HRMS m/z calcd for $C_{15}H_{15}N$ 209.1204 (M^+), found 209.1206.

5-Bromo-2-(1-hexynyl)pyridine (16): R_f = 0.27 (10% Et_2O in hexane); IR (neat) 2958, 2872, 2228, 1564, 1544 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (1H, d, J = 2.1 Hz), 7.74 (1H, dd, J = 8.4 and 2.1 Hz), 7.25 (1H, d, J = 8.4 Hz), 2.43 (2H, t, J = 7.2 Hz), 1.66−1.55 (2H, m), 1.54−1.42 (2H, m), 0.94 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 142.3, 138.6, 127.7, 119.3, 92.6, 79.5, 30.2, 22.0, 19.0, 13.6; MS m/z 237 (M^+); HRMS m/z calcd for $C_{11}H_{12}NBr$ 237.0153 (M^+), found 237.0148.

2-(3-phenylpropynyl)pyridine (22): R_f = 0.36 (50% Et_2O in hexane); IR (neat) 3029, 2228, 1582, 1558 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56−8.54 (1H, m), 7.60 (1H, ddd, J = 7.8, 7.6, and 1.8 Hz), 7.43−7.39 (3H, m), 7.35−7.30 (2H, m), 7.27−7.16 (2H, m), 3.86 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 143.5, 136.0, 135.8, 128.5, 128.5, 127.9, 127.9, 126.8, 126.7, 122.4, 88.0, 82.1, 25.5; MS m/z 193 (M^+); HRMS m/z calcd for $C_{14}H_{11}N$ 193.0891 (M^+), found 191.0885.

2-(5-Hydroxypentynyl)pyridine (24): R_f = 0.37 (100% AcOEt); IR (neat) 3338, 2944, 2873, 2225, 1585, 1560 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52−8.50 (1H, m), 7.65−7.58 (1H, m), 7.38−7.35 (1H, m), 7.21−7.16 (1H, m), 3.81 (2H, t, J = 6.0 Hz), 3.30 (1H, brs) 2.58 (2H, t, J = 6.9 Hz), 1.88 (2H, dt, J = 6.9 and 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 143.5, 136.2, 126.8, 122.4, 90.6, 80.4, 61.0, 30.9, 15.8; MS m/z 161 (M^+); HRMS m/z calcd for $C_{10}H_{11}NO$ 161.0841 (M^+), found 161.0836.

2-(4-Hydroxybutynyl)pyridine (25): R_f = 0.31 (100% AcOEt); IR (neat) 3353, 2238, 1588, 1563 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (1H, dd, J = 4.8 and 1.5 Hz), 7.63 (1H, ddd, J = 7.8, 7.8, and 1.5 Hz), 7.37 (1H, d, J = 7.8 Hz), 7.22−7.18 (1H, m), 4.05 (1H, brs), 3.88 (2H, t, J = 6.3 Hz), 2.71 (2H, t, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 143.1, 136.4, 126.7, 122.5, 88.6, 81.2, 60.4, 23.7; MS m/z 147 (M^+); HRMS m/z calcd for C_9H_9NO 147.0684 (M^+), found 147.0678.

2,6-Di-1-hexynylpyridine (29): R_f = 0.27 (10% Et_2O in hexane); IR (neat) 2958, 2872, 2231, 1574, 1563, 1558 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, dd, J = 7.5 and 7.5 Hz), 7.22 (2H, d, J = 7.5 Hz), 2.41 (4H, t, J = 7.2 Hz), 1.64−1.52 (4H, m), 1.52−1.40 (4H, m), 0.93 (6H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 135.9, 125.1, 91.1, 80.0, 30.4, 22.1, 19.0, 13.6; MS m/z 239 (M^+); HRMS m/z calcd for $C_{17}H_{21}N$ 239.1674 (M^+), found 239.1664.

2,5-Di-1-hexynylpyridine (30): R_f = 0.24 (10% Et_2O in hexane); IR (neat) 2958, 2872, 2230, 1584, 1538 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (1H, d, J = 1.8 Hz), 7.58 (1H, dd, J = 8.4 and 1.8 Hz), 7.27 (1H, d, J = 8.4 Hz), 2.44 (2H, t, J = 6.9 Hz), 2.43 (2H, t, J = 6.9 Hz), 1.66−1.41 (8H, m), 0.95 (3H, t, J = 7.2 Hz), 0.94 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 141.8, 138.3, 125.8, 119.6, 95.3, 92.5, 80.2, 77.3, 30.5, 30.3, 22.0, 21.9, 19.1, 19.0, 13.5, 13.5; MS m/z 239 (M^+); HRMS m/z calcd for $C_{17}H_{21}N$ 239.1674 (M^+), found 239.1664.

2-(5-*tert*-Butyldimethylphenylsiloxy-1-pentynyl)pyridine (27). To a stirred solution of alcohol **24** (9.60 mL, 94.7 mmol), imidazole (7.62 g, 112 mmol), and a catalytic amount of DMAP in DMF (120 mL) was added dropwise TBDPSCl (28.6 mL, 98.0 mmol) at room temperature, and stirring was continued for 2 h. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and NaCl. The residue upon workup was purified by chromatography on silica gel with hexane−AcOEt (95:5 v/v) as eluent to give the silyl ether **27** (32.2 g, 99%) as a colorless oil: R_f = 0.27 (50% Et_2O in hexane); IR (neat) 3076, 2930, 2855, 2229, 1583 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (1H, dd, J = 4.2 and 1.8 Hz), 7.68−7.64 (4H, m), 7.56 (1H, ddd, J = 7.5, 7.5, and 1.8 Hz), 7.41−7.30 (6H, m), 7.28 (1H, d, J = 7.5 Hz), 7.14 (1H, dd, J = 7.5 and 4.2 Hz), 3.79 (2H, t, J = 6.0 Hz), 2.60 (2H, t, J = 7.2 Hz), 1.88 (2H, dt, J = 7.2 and 6.0 Hz), 1.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 143.7, 135.8, 135.4, 135.4, 135.4, 135.4, 133.6, 133.6, 129.4, 129.4, 127.5, 127.5, 127.5, 127.5, 126.7, 122.1, 90.6, 80.4, 62.4, 31.4, 26.9, 26.9, 26.9, 19.3, 16.0; MS m/z 342 ($M^+ - C_4H_9$); HRMS m/z calcd for $C_{22}H_{20}NOSi$ 342.1328 ($M^+ - C_4H_9$), found 342.1321.

2-(1-*tert*-Butyldimethylsiloxy-1-methyl-2-heptynyl)-pyridine (54). To a stirred solution of 1-hexyne (4.1 mL, 35.6 mmol) in THF (80 mL) was added TMEDA (5.4 mL, 35.6 mmol), and a 2.5 M solution of *n*-BuLi in hexane (14.2 mL, 35.6 mmol) was added dropwise at −78 °C. After stirring was continued for 1 h, 2-acetylpyridine **52** (2.0 mL, 17.8 mmol) was added dropwise to this reaction mixture at the same temperature, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. To a solution of the residue upon workup in CH_2Cl_2 (70 mL) were added pyridine (5.05 mL, 62.4 mmol) and TBSOTf (7.01 mL, 30.50 mmol) at 0 °C. After stirring was continued for 1 h at the same temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$ and NaCl. The residue upon workup was purified by chromatography on silica gel with hexanes:Et_2O (70:30 v/v) as eluent to give the alkyne **54** (5.54 g, 2 steps 86%) as a colorless oil: R_f = 0.68 (50% Et_2O in hexane); IR (neat) 2958, 2931, 2858, 2247, 1587 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56−8.54 (1H, m), 7.69−7.61 (2H, m), 7.12−7.09 (1H, m), 2.24−2.19 (2H, m), 1.78 (3H, s), 1.50−1.45 (2H, m), 1.39−1.33 (2H, m), 0.94 (9H, s), 0.86 (3H, t, J = 7.2 Hz), 0.24 (3H, s), 0.15 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 148.5, 136.4, 121.8, 118.8, 85.8, 83.8, 72.1, 32.9, 30.5, 25.8, 25.8, 22.0, 18.6, 18.1, 13.5, −2.9, −3.2; MS m/z (M^+); HRMS m/z calcd for $C_{19}H_{31}NOSi$ 317.2175 (M^+), found 317.2190.

2-(1-*tert*-Butyldimethylsiloxy-1-methyl-2-heptynyl)-pyrazine (55). By following the same procedure described for **54**, the alkyne **55** was prepared from **53**: yield 89%; R_f = (50% Et_2O in hexane); IR (neat) 3051, 2957, 2249, 1471 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (1H, s), 8.50 (1H, d, J = 2.4 Hz), 8.45 (1H, d, J = 2.4 Hz), 2.24 (2H, t, J = 6.9 Hz), 1.82 (3H, s), 1.55−1.33 (4H, m), 0.95 (9H, s), 0.90 (3H, t, J = 7.2 Hz), 0.28 (3H, s), 0.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 142.7, 142.6, 141.7, 87.0, 82.9, 71.2, 32.7, 30.6, 26.0, 26.0, 26.0, 22.2, 18.8, 18.4, 13.8, −2.6, −2.9; MS m/z (M^+); HRMS m/z calcd for $C_{17}H_{27}NOSi$ 303.1893 (M^+), found 303.1890.

2-(1-*tert*-Butyldimethylsiloxy-1-methyl-3-butynyl)-pyridine (56). A suspension of powdered aluminum (445 mg,

16.50 mmol) and mercuric chloride (179 mg, 0.66 mmol) in THF (40 mL) was refluxed for 30 min. After the mixture was cooled to room temperature, propargyl bromide (1.47 mL, 16.50 mmol) was added dropwise to the suspension, and the mixture was stirred at same temperature for 6 h. The above propargylaluminum reagent was added dropwise to the acetylpyridine **52** (800 mg, 6.60 mmol) in Et_2O (40 mL) at 0 °C, and stirring was continued for 1 h. The reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. Pyridine (0.752 mL, 9.30 mmol) and TBSOTf (1.59 mL, 6.96 mmol) were added to a solution in CH_2Cl_2 (50 mL) of the residue following workup at 0 °C. After stirring was continued for 1 h at the same temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$ and NaCl. The residue upon workup chromatographed on silica gel with hexane:AcOEt (70:30 v/v) as eluent to give the alkyne **56** (1.20 g, two steps 66%) as a colorless oil: $R_f = 0.68$ (50% Et_2O in hexane); IR (neat) 3313, 2957, 2930, 2857, 2122, 1590, 1572 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54−8.52 (1H, m), 7.74−7.66 (2H, m), 7.18−7.13 (1H, m), 2.87 (1H, dd, J = 16.5 and 2.7 Hz), 2.75 (1H, dd, J = 16.5 and 2.7 Hz), 1.86 (1H, d, J = 2.7 Hz), 1.73 (3H, s), 0.99 (9H, s), 0.21 (3H, s), 0.10 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 148.0, 136.4, 121.8, 120.2, 81.4, 77.9, 70.3, 34.3, 28.3, 26.0, 26.0, 26.0, 18.5, −2.2, −2.3; MS m/z 260 ($M^+ - CH_3$); HRMS m/z calcd for $C_{15}H_{22}NOSi$ 260.1471 ($M^+ - CH_3$), found 260.1473.

2-(1-*tert*-Butyldimethylsiloxy-1-methyl-3-pentynyl)-pyridine (57). To a stirred solution of alkyne **56** (120 mg, 0.436 mmol) in THF (10 mL) was added a 2.0 M solution of *n*-BuLi in hexane (0.218 mL, 0.436 mmol) dropwise at −78 °C. After stirring was continued for 1 h, methyl bromide (0.50 mL, 1.09 mmol) was added dropwise to this reaction mixture at the same temperature, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon workup was purified by chromatography on silica gel with hexanes:Et_2O (80:20 v/v) as eluent to give the alkyne **57** (122 mg, 97%) as a colorless oil: $R_f = 0.73$ (50% Et_2O in hexane); IR (neat) 2957, 2929, 2857, 1590, 1572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53−8.48 (1H, m), 7.70−7.61 (2H, m), 7.13−7.07 (1H, m), 2.71−2.67 (2H, m), 1.67 (3H, s), 1.66 (3H, t, J = 3.0 Hz), 0.95 (9H, s), 0.17 (3H, s), 0.05 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 148.0, 136.0, 121.5, 120.1, 78.2, 77.5, 76.1, 34.5, 28.1, 26.0, 26.0, 26.0, 18.4, 3.5, −2.3, −2.3; MS m/z 274 ($M^+ - CH_3$); HRMS m/z calcd for $C_{16}H_{24}NOSi$ 274.1627 ($M^+ - CH_3$), found 274.1634.

General Procedure for the Rhodium-Catalyzed Addition Reaction of Arylboronic Acids to Alkynes (Entry 2 in Table 2). To a stirred mixture of $[Rh(COD)Cl]_2$ (3.2 mg, 6.42 μmol) and **3** (12.8 mg, 25.7 μmol) in H_2O (2 mL) were successively added 2-methylphenylboronic acid (109 mg, 0.802 mmol), SDS (52 mg, 0.160 mmol), Na_2CO_3 (68 mg, 0.642 mmol), and alkyne **11** (47.9 mg, 0.301 mmol) at room temperature. After stirring was continued for 1 h at 80 °C, the reaction mixture was poured into Et_2O (25 mL) and the heterogeneous mixture was vigorously stirred for 1 h at room temperature. The two phases were separated, and the aqueous phase was extracted with Et_2O. The residue upon workup was chromatographed on silica gel with hexanes:Et_2O (85:15 v/v) as eluent to give the product **32b** (61.0 mg, 81%) as a colorless oil.

(*E*)-2-(2-Phenyl-1-hexenyl)pyridine (32a): $R_f = 0.72$ (50% Et_2O in hexane); IR (neat) 2956, 2858, 1626, 1584, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (1H, dd, J = 4.5 and 1.8 Hz), 7.64 (1H, ddd, J = 7.8, 7.8, and 1.5 Hz), 7.52−7.49 (2H, m), 7.39−7.25 (4H, m), 7.10 (1H, dd, J = 7.8 and 4.5 Hz), 6.70 (1H, s), 3.05 (2H, t, J = 7.5 Hz), 1.48−1.26 (4H, m), 0.84 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 149.2, 147.5, 143.2, 135.9, 128.3, 128.3, 127.4, 127.1, 126.7, 126.7, 124.2, 120.9, 30.8, 30.0, 22.7, 13.8; MS m/z 237 (M^+); HRMS m/z calcd for $C_{17}H_{19}N$ 237.1517 (M^+), found 237.1525.

(*E*)-2-[2-(2-Methylphenyl)-1-hexenyl]pyridine (32b): $R_f = 0.71$ (50% Et_2O in hexane); IR (neat) 2956, 2870, 1634, 1585, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.65−8.63 (1H, m), 7.64 (1H, ddd, J = 7.8, 7.5, and 1.5 Hz), 7.26−7.18 (5H, m), 7.13−7.09 (1H, m), 6.35 (1H, s), 2.90 (2H, t, J = 7.5 Hz), 2.37 (3H, s), 1.44−1.23 (4H, m), 0.83 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.2, 148.4, 144.1, 135.9, 134.9, 130.1, 128.4, 128.3, 126.8, 125.3, 124.0, 120.9, 32.5, 30.1, 22.9, 20.0, 13.8; MS m/z 251 (M^+); HRMS m/z calcd for $C_{18}H_{21}N$ 251.1674 (M^+), found 251.1679.

(*E*)-2-[2-(2,6-Dimethylphenyl)-1-hexenyl]pyridine (32c): $R_f = 0.75$ (50% Et_2O in hexane); IR (neat) 2956, 2858, 1634, 1583, 1558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, dd, J = 4.5 and 1.5 Hz), 7.65 (1H, ddd, J = 7.8, 7.8, and 1.5 Hz), 7.25 (1H, d, J = 7.8 Hz), 7.13−7.04 (4H, m), 6.30 (1H, s), 2.86 (2H, t, J = 7.4 Hz), 2.32 (3H, s), 2.32 (3H, s), 1.46−1.24 (4H, m), 0.86 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.3, 147.2, 143.6, 135.9, 135.9, 135.2, 128.4, 127.4, 127.4, 126.4, 123.9, 120.9, 33.2, 30.1, 23.3, 20.4, 20.4, 13.9; MS m/z 265 (M^+); HRMS m/z calcd for $C_{19}H_{23}N$ 265.1830 (M^+), found 265.1825.

(*E*)-2-[2-(1-Naphthyl)-1-hexenyl]pyridine (32d): $R_f = 0.66$ (50% Et_2O in hexane); IR (neat) 3058, 2956, 2870, 1634, 1584, 1558, 1505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (1H, dd, J = 4.5 and 1.8 Hz), 8.13−8.08 (1H, m), 7.87−7.83 (1H, m), 7.78 (1H, d, J = 8.1 Hz), 7.64 (1H, ddd, J = 7.5, 7.5, and 1.8 Hz), 7.49−7.44 (3H, m), 7.38 (1H, dd, J = 7.2 and 1.2 Hz), 7.28 (1H, d, J = 7.2 Hz), 7.12 (1H, dd, J = 7.5 and 4.5 Hz), 6.55 (1H, s), 3.10 (2H, t, J = 7.8 Hz), 1.45−1.22 (4H, m), 0.79 (3H, t, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 149.3, 147.4, 142.4, 136.0, 133.7, 131.4, 129.4, 128.2, 127.2, 126.0, 125.7, 125.6, 125.2, 125.1, 124.2, 121.1, 33.3, 30.5, 22.8, 13.8; MS m/z 287 (M^+); HRMS m/z calcd for $C_{21}H_{21}N$ 287.1674 (M^+), found 287.1669.

(*E*)-2-[2-(4-Methoxyphenyl)-1-hexenyl]pyridine (32e): $R_f = 0.54$ (50% Et_2O in hexane); IR (neat) 2955, 2857, 1605, 1583, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, dd, J = 4.2 and 1.8 Hz), 7.64 (1H, ddd, J = 7.5, 7.5, and 1.8 Hz), 7.48−7.42 (2H, m), 7.26 (1H, d, J = 7.5 Hz), 7.09 (1H, dd, J = 7.5 and 4.5 Hz), 6.93−6.88 (2H, m), 6.66 (1H, s), 3.83 (3H, s), 3.01 (2H, t, J = 6.9 Hz), 1.48−1.26 (4H, m), 0.85 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 157.3, 149.2, 146.9, 135.9, 135.4, 127.7, 127.7, 125.8, 124.1, 120.8, 113.7, 113.7, 55.2, 30.9, 29.9, 22.7, 13.9; MS m/z 267 (M^+); HRMS m/z calcd for $C_{18}H_{21}NO$ 267.1623 (M^+), found 267.1622.

(*E*)-2-[2-(4-Methoxy-2-methylphenyl)-1-hexenyl]pyridine (32f): $R_f = 0.42$ (50% Et_2O in hexane); IR (neat) 2956, 2857, 1634, 1606, 1584, 1504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.61−8.59 (1H, m), 7.62 (1H, ddd, J = 7.8, 7.8, and 2.1 Hz), 7.22 (1H, d, J = 7.8 Hz), 7.10−7.06 (2H, m), 6.75−6.69 (2H, m), 6.31 (1H, s), 3.80 (3H, s), 2.86 (2H, t, J = 7.2 Hz), 2.34 (3H, s), 1.41−1.23 (4H, m), 0.83 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.9, 149.1, 148.0, 136.6, 136.3, 135.8, 129.3, 128.5, 123.9, 120.8, 115.4, 110.5, 55.2, 32.8, 30.2, 23.0, 20.4, 14.0; MS m/z 281 (M^+); HRMS m/z calcd for $C_{19}H_{23}NO$ 281.1780 (M^+), found 281.1775.

(*E*)-2-[2-(2-Methylphenyl)-1-hexenyl]pyrimidine (35): $R_f = 0.69$ (50% Et_2O in hexane); IR (neat) 2957, 2870, 1634, 1568, 1553 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.73 (2H, d, J = 4.8 Hz), 7.21−7.18 (4H, m), 7.04 (1H, dd, J = 4.8 and 4.8 Hz), 6.46 (1H, s), 3.13 (2H, t, J = 7.5 Hz), 2.37 (3H, s), 1.46−1.26 (4H, m), 0.85 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 156.6, 156.6, 154.7, 144.1, 134.6, 130.1, 128.1, 127.8, 126.9, 125.3, 117.6, 32.8, 30.0, 22.9, 19.9, 13.8; MS m/z 252 (M^+); HRMS m/z calcd for $C_{17}H_{20}N_2$ 252.1626 (M^+), found 252.1632.

(*E*)-2-[2-(2-Methylphenyl)-1-hexenyl]quinoline (36): $R_f = 0.55$ (10% Et_2O in hexane); IR (neat) 3057, 2955, 2857, 1596, 1557, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (1H, d, J = 3.6 Hz), 8.06 (1H, d, J = 3.6 Hz), 7.75 (1H, d, J = 8.0 Hz),

7.70−7.66 (1H, m), 7.49−7.45 (1H, m), 7.35 (1H, d, J = 8.0 Hz), 7.24−7.17 (4H, m), 6.50 (1H, s), 3.06 (2H, t, J = 8.0 Hz), 2.39 (3H, s), 1.54−1.46 (2H, m), 1.43−1.33 (2H, m), 0.89 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 150.7, 148.1, 144.3, 135.7, 134.9, 130.2, 129.4, 129.3, 128.4, 128.4, 127.3, 126.9, 126.4, 125.9, 125.4, 122.8, 33.1, 30.2, 23.1, 20.0, 14.0; MS m/z 301 (M^+); HRMS m/z calcd for $C_{22}H_{23}N$ 301.1830 (M^+), found 301.1837.

(*E*)-5-Bromo-2-[2-(2-methylphenyl)-1-hexenyl]pyridine (37): R_f = 0.61 (10% Et_2O in hexane); IR (neat) 2956, 2857, 1634, 1568 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, d, J = 2.7 Hz), 7.73 (1H, dd, J = 8.1 and 2.7 Hz), 7.19−7.08 (5H, m), 6.24 (1H, s), 2.88 (2H, t, J = 7.5 Hz), 2.34 (3H, s), 1.43−1.22 (4H, m), 0.84 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 150.1, 149.8, 143.9, 138.4, 134.7, 130.1, 128.2, 126.8, 126.8, 125.3, 125.2, 117.7, 32.8, 30.1, 23.0, 20.0, 14.0; MS m/z 329 (M^+); HRMS m/z calcd for $C_{18}H_{20}NBr$ 329.0779 (M^+), found 329.0787.

(*E*)-2-[2-(2-Methylphenyl)-3-phenyl-1-propenyl]pyridine (38): R_f = 0.71 (50% Et_2O in hexane); IR (neat) 3060, 3025, 2922, 1634, 1585, 1558 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68−8.67 (1H, m), 7.65 (1H, ddd, J = 7.6, 7.6, and 1.6 Hz), 7.25 (1H, d, J = 7.6 Hz), 7.16−6.98 (10H, m), 6.43 (1H, s), 4.43 (2H, s), 2.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 149.2, 146.1, 143.4, 139.3, 136.2, 135.1, 130.1, 129.3, 129.3, 128.9, 128.7, 128.0, 128.0, 126.8, 125.8, 125.2, 124.4, 121.4, 38.4, 19.7; MS m/z 285 (M^+); HRMS m/z calcd for $C_{21}H_{19}N$ 285.1517 (M^+), found 285.1513.

(*E*)-2-[5-*tert*-Butyldimethylsiloxy-2-(2-methylphenyl)-1-pentenyl]pyridine (40): R_f = 0.57 (50% Et_2O in hexane); IR (neat) 3070, 2930, 2857, 1634, 1585, 1558 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58−8.55 (1H, m), 7.61−7.52 (5H, m), 7.39−7.24 (7H, m), 7.19−7.11 (4H, m), 7.07−7.02 (1H, m), 6.36 (1H, s), 3.64 (2H, t, J = 6.0 Hz), 3.04−2.99 (2H, m), 2.34 (3H, s), 1.71−1.62 (2H, m), 1.00 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 149.1, 147.7, 143.7, 135.8, 135.4, 135.4, 135.4, 135.4, 134.8, 133.8, 133.8, 130.0, 129.3, 129.3, 128.6, 128.4, 127.4, 127.4, 127.4, 127.4, 126.8, 125.3, 123.9, 120.9, 63.9, 31.0, 29.4, 26.9, 26.9, 26.9, 20.1, 19.3; MS m/z 491 (M^+); HRMS m/z calcd for $C_{33}H_{37}NOSi$ 491.2644 (M^+), found 491.2658.

(*E*)-2-[5-Hydroxy-2-(2-methylphenyl)-1-pentenyl]pyridine (41): R_f = 0.34 (50% AcOEt in hexane); IR (neat) 3286, 2932, 1634, 1589, 1563 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (1H, dd, J = 5.2 and 1.2 Hz), 7.69 (1H, ddd, J = 7.9, 7.9, and 1.2 Hz), 7.22−7.13 (6H, m), 6.53 (1H, brs), 6.43 (1H, s), 3.74 (2H, t, J = 5.2 Hz), 3.09 (2H, t, J = 6.4 Hz), 2.36 (3H, s), 1.63 (2H, dt, J = 6.4 and 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 148.1, 147.6, 143.0, 137.1, 134.9, 130.5, 129.0, 128.4, 127.1, 125.5, 125.4, 121.6, 59.6, 29.2, 27.7, 19.8; MS m/z 253 (M^+); HRMS m/z calcd for $C_{17}H_{19}NO$ 253.1467 (M^+), found 253.1474.

(*E*)-2-[4-Hydroxy-2-(2-methylphenyl)-1-butenyl]pyridine (42): R_f = 0.44 (50% Et_2O in hexane); IR (neat) 3242, 2853, 1634, 1590, 1562 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (1H, dd, J = 5.1 and 1.8 Hz), 7.71 (1H, ddd, J = 7.8, 7.8, and 1.8 Hz), 7.26−7.19 (6H, m), 7.01 (1H, brs), 6.56 (1H, s), 3.81 (2H, t, J = 5.7 Hz), 2.98 (2H, t, J = 5.7 Hz), 2.38 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 147.7, 146.4, 143.3, 137.1, 135.2, 130.2, 129.5, 128.6, 127.2, 125.4, 124.6, 122.0, 60.3, 35.7, 19.8; MS m/z 239 (M^+); HRMS m/z calcd for $C_{16}H_{17}NO$ 239.1310 (M^+), found 239.1304.

(*E,E*)-2,6-Bis[2-(2-methylphenyl)-1-hexenyl]pyridine (43): R_f = 0.61 (10% Et_2O in hexane); IR (neat) 3015, 2956, 2858, 1634, 1558 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, dd, J = 7.8 and 7.8 Hz), 7.21−7.14 (8H, m), 7.08 (2H, d, J = 7.8 Hz), 6.36 (2H, s), 2.93 (4H, t, J = 7.2 Hz), 2.37 (6H, s), 1.43−1.23 (8H, m), 0.82 (6H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 147.8, 144.2, 135.8, 134.9, 130.0, 128.8, 128.4, 126.6, 125.2, 121.4, 32.7, 30.3, 23.1, 20.1, 14.1; MS m/z 423 (M^+); HRMS m/z calcd for $C_{31}H_{37}N$ 423.2926 (M^+), found 423.2915.

(*E*)-5-(1-Hexynyl)-2-[2-(2-methylphenyl)-1-hexenyl]-pyridine (44): R_f = 0.56 (10% Et_2O in hexane); IR (neat) 2957, 2871, 2230, 1634, 1587, 1538 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, d, J = 1.5 Hz), 7.60 (1H, dd, J = 8.1 and 1.5 Hz), 7.20−7.11 (5H, m), 6.28 (1H, s), 2.90 (2H, t, J = 7.2 Hz), 2.44 (2H, t, J = 6.9 Hz), 2.34 (3H, s), 1.65−1.55 (2H, m), 1.55−1.43 (2H, m), 1.41−1.23 (4H, m), 0.96 (3H, t, J = 7.2 Hz), 0.83 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 151.6, 149.2, 144.1, 138.2, 134.8, 130.0, 128.3, 127.8, 126.7, 125.3, 123.2, 118.1, 93.7, 77.8, 32.8, 30.8, 30.2, 23.0, 22.1, 20.1, 19.3, 14.0, 13.7; MS m/z 331 (M^+); HRMS m/z calcd for $C_{24}H_{29}N$ 331.2300 (M^+), found 331.2300.

(*E*)-2-[1-Deuterio-2-(2-methylphenyl)-1-hexenyl]pyridine (49): R_f = 0.71 (50% Et_2O in hexane); IR (neat) 3058, 2956, 2927, 2870, 1622, 1585, 1558 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63−8.60 (1H, m), 7.62 (1H, ddd, J = 7.8, 7.8, and 1.5 Hz), 7.24−7.15 (5H, m), 7.08 (1H, ddd, J = 7.8, 4.8, and 1.8 Hz), 2.90 (2H, t, J = 7.8 Hz), 2.36 (3H, s), 1.42−1.23 (4H, m), 0.83 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 149.1, 148.3, 144.0, 135.8, 134.8, 130.0, 128.3, 127.5(t), 126.7, 125.2, 123.9, 120.9, 32.5, 30.2, 23.0, 20.1, 14.0; MS m/z 252 (M^+); HRMS m/z calcd for $C_{18}H_{20}DN$ 252.1736 (M^+), found 252.1738.

(*E*)-2-[1-*tert*-Butyldimethylsiloxy-1-methyl-3-(2-methylphenyl)-2-heptenyl]pyridine (58): R_f = 0.65 (25% Et_2O in hexane); IR (neat) 3058, 2955, 2857, 1729, 1644, 1587 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.56 (1H, m), 7.86 (1H, d, J = 8.0 Hz), 7.69 (1H, ddd, J = 8.0, 8.0, and 1.6 Hz), 7.16−7.10 (4H, m), 7.07−7.05 (1H, m), 5.77 (1H, s), 2.31 (3H, s), 2.29 (1H, dt, J = 12.8 and 4.4 Hz), 1.98 (1H, dt, J = 12.8 and 4.4 Hz), 1.84 (3H, s), 1.01 (9H, s), 0.92−0.68 (4H, m), 0.57 (3H, t, J = 7.2 Hz), 0.19 (3H, s), 0.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 148.0, 143.7, 143.3, 137.7, 135.9, 135.5, 129.9, 128.5, 126.3, 125.1, 121.1, 120.4, 77.6, 32.7, 31.7, 28.6, 26.1, 26.1, 26.1, 22.9, 19.8, 18.4, 13.7, −2.1, −2.2; MS m/z 409 (M^+); HRMS m/z calcd for $C_{26}H_{39}NOSi$ 409.2801 (M^+), found 409.2811.

(*E*)-2-[1-*tert*-Butyldimethylsiloxy-1-methyl-3-(2-methylphenyl)-2-heptenyl]pyrazine (59): R_f = 0.68 (50% Et_2O in hexane); IR (neat) 2957, 2858, 1644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (1H, s), 8.50 (1H, d, J = 2.4 Hz), 8.44 (1H, d, J = 2.4 Hz), 7.15−7.02 (4H, m), 5.73 (1H, s), 2.31−2.21 (1H, m), 2.28 (3H, s), 2.04−1.94 (1H, m), 1.82 (3H, s), 0.99 (9H, s), 0.90−0.66 (3H, m), 0.56 (3H, t, J = 7.2 Hz), 0.39−0.25 (1H, m), 0.19 (3H, s), 0.09 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 144.2, 143.1, 143.0, 142.6, 142.0, 136.6, 135.3, 130.0, 128.3, 126.5, 125.2, 76.8, 32.8, 31.7, 28.7, 26.0, 26.0, 26.0, 22.8, 19.8, 18.3, 13.7, −2.1, −2.2; MS m/z (M^+); HRMS m/z calcd for $C_{25}H_{38}N_2OSi$ 410.2753 (M^+), found 410.2757.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectrum of **12**−**16**, **22**, **24**, **25**, **27**, **29**, **30**, **32a**−**f**, **35**−**44**, **49**, and **54**−**60** and ROESY spectrum of **32e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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