Addition of Heteroaromatics to Alkylidenecyclopropanes Catalyzed by Palladium

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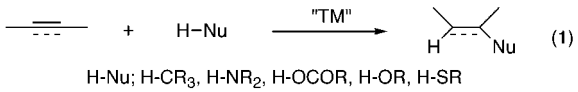
Received January 9, 2002

The reaction of heteroaromatics, such as furans, thiophenes, thiazoles, and pyrroles, with alkylidenecyclopropanes proceeded smoothly in the presence of palladium catalysts, producing the corresponding α-allylated products in good to high yields. For example, the reaction of 3-butylpentylidenecyclopropane (**1a**) with 2-methylfuran (**2a**), ethyl 2-thiophenecarboxylate (**4a**), 2-isobutylthiazole (**6a**), and 1-methylpyrrole (**11b**) gave the α-allylated products in 70%, 66%, 77%, and 30% yield, respectively. The reaction proceeded predominantly through distal bond cleavage. The order of reactivity of heteroaromatics toward **1a** is as follows: furan > thiophene ≈ thiazole (5-position) > thiazole (2-position) ≈ pyrrole. This methodology provides a means for introducing an allylic group to various kinds of heteroaromatics under mild conditions.

Introduction

The addition of *nucleophiles* ($^-$Nu) to carbon−carbon multiple bonds coordinated to Pd(II) is one of the most popular processes for palladium-catalyzed organic transformations.[1] However, the palladium-catalyzed addition of *pronucleophiles* (H−Nu) to carbon−carbon multiple bonds has not been investigated widely.[2−7] The additions of carbon pronucleophiles (H−CR_3, hydrocarbonation),[3] nitrogen pronucleophiles (H−NR_2, hydroamination),[4] oxygen pronucleophiles (H−OR, hydroalkoxylation),[5] carboxyl pronucleophiles (H−OCOR, hydrocarboxylation),[6] and sulfur pronucleophiles (H−SR, hydrosulfination)[7] to C−C multiple bonds are catalyzed by palladium and other transition-metal complexes (eq 1).



Allenes, 1,3-dienes, alkynes, 1,3-enynes, 1,3-diynes, and styrenes have been utilized as substrates having a C−C multiple bond. Recently, we reported that methyl-

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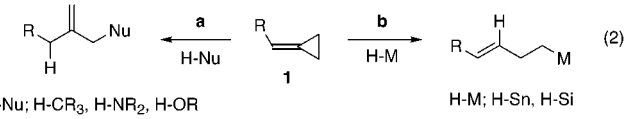
10.1021/jo0255126 CCC: $22.00
Published on Web 04/18/2002

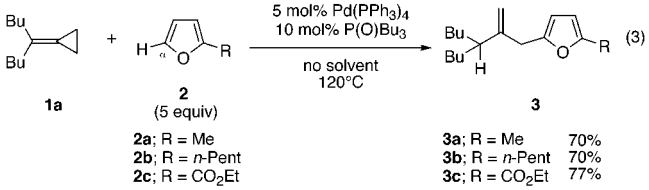
enecyclopropanes could become useful acceptors for the palladium-catalyzed pronucleophile addition, and the hydrocarbonation,[8] hydroamination,[9] and hydroalkoxylation[10] gave the corresponding ring-opening allylic derivatives in good to high yields (eq 2, path a).



(2)

Actually, methylenecyclopropanes are interesting substrates for the transition-metal-catalyzed reactions; they are rather stable, easily accessible, and easy to handle despite a high level of ring strain.[11] In early 1970, transition-metal-catalyzed [3 + 2] cycloaddition of alkylidenecyclopropanes with olefins was well investigated and became a powerful tool to construct five-membered carbocycles.[12] In the past decade, catalytic ring-opening reactions of alkylidenecyclopropanes **1** involving the addition of organometallic compounds were reported (eq 2).[13−15] It was demonstrated that the palladium-catalyzed hydrostannation[13] and the rhodium-catalyzed hydrosilylation[14] proceeded through proximal bond cleavage (path b). On the other hand, as mentioned above, the palladium-catalyzed hydrocarbonation,[8] hydroamination,[9] and hydroalkoxylation[10] mainly or predominantly proceeded through distal bond cleavage, giving the corresponding allylated products (path a).

In the course of this study, we discovered that in the presence of palladium catalysts alkylidenecyclopropanes **1** reacted with furans **2** at the α-position, producing the corresponding α-allylated furans **3** in good to high yields (eq 3).[16] This reaction, so-called *hydrofurylation*, proceeds through the selective ring opening of **1** at a distal bond.



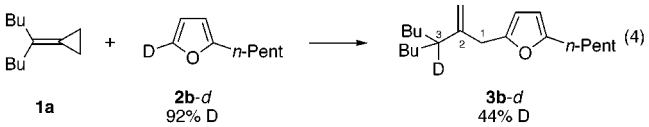
(3)

In this paper, we report the full details of the addition of furans together with the addition of heteroaromatics,[17] such as thiophenes, thiazoles, and pyrroles, to alkylidenecyclopropanes **1.**

Results

Addition of Furans 2 to Alkylidenecyclopropanes 1 Catalyzed by Palladium (Hydrofurylation).[16] The palladium-catalyzed addition of furans **2** with alkylidenecyclopropanes **1** proceeded smoothly (eq 3). The reaction of 2-butylpentylidenecyclopropane (**1a**) (0.5 mmol) and 2-methylfuran **(2a**) (2.5 mmol) in the presence of 5 mol % $Pd(PPh_3)_4$ and 10 mol % tributylphosphine oxide proceeded smoothly at 120 °C without solvent to give the corresponding α-allylated furan **3a** in 70% yield. Other catalysts such as $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd(OAc)_2$, and $Pt(PPh_3)_4$ did not promote the reaction at all. The choice of phosphine ligands is very important. Among numerous phosphine ligands examined, *tributylphosphine oxide* gave the best result; the use of other ligands afforded unsatisfactory results, and in the absence of tributylphosphine oxide the reaction was very slow. The reaction of **1a** with 2-pentylfuran (**2b)** and ethyl 2-furoate (**2c**) produced **3b** and **3c** in 70% and 77% yield, respectively.

To determine the fate of the C−H at the 2-position of furans, we carried out the reaction of 2-deuterio-5-pentylfuran (**2b**-*d*) (D content 92%) with **1a** under the same conditions as above. The monodeuterated **3b**-*d*, in which the deuterium content at the C-3 position was 44%, was obtained in 66% yield (eq 4). The other positions were not deuterated at all.



(4)

Addition of Thiophenes. The reaction of the thiophene derivatives **4** with **1** was examined (eq 5), and the results are summarized in Table 1. In the presence of

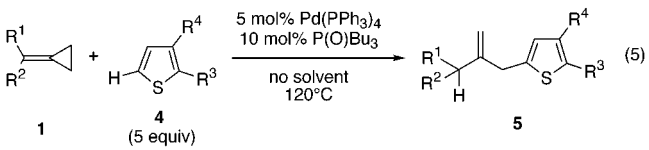


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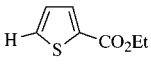
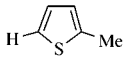
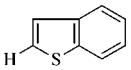
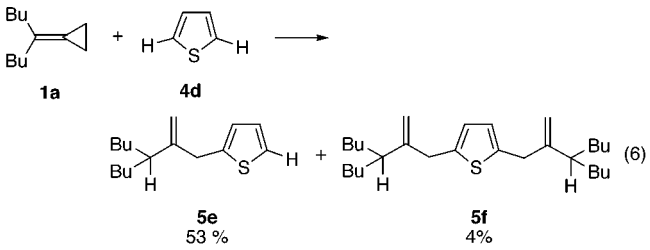
Table 1. Addition of Thiophenes 4 to Alkylidenecyclopropanes 1[a]

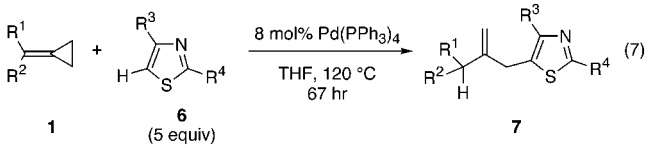
entry	1	4	time / h	5	yield / %[b]
1	 **1a**	 **4a**	42	**5a**	66
2	 **1b**	**4a**	45	**5b**	66
3	**1a**	 **4b**	68	**5c**	49
4	**1a**	 **4c**	86	**5d**	58

[a] The reaction of alkylidenecyclopropanes **1** (0.5 mmol) with thiophenes **4** (2.5 mmol) was carried out in the presence of 5 mol % $Pd(PPh_3)_4$ and 10 mol % tributylphosphone oxide without solvent at 120 °C. [b] Isolated yield based on **1**.

catalytic amounts of $Pd(PPh_3)_4$ (5 mol %) and tributylphosphine oxide (10 mol %), the reaction of ethyl 2-thiophenecarboxylate (**4a**) with **1a** produced the corresponding 2-allylthiophene derivative **5a** in 66% yield (entry 1). 2-Hexylheptylidenecyclopropane (**1b**) and **4a** reacted smoothly, giving **5b** in 66% yield (entry 2). The reaction of **1a** with 2-methylthiophene (**4b**) and thianaphthene (**4c**) afforded **5c** and **5d**, respectively, in good yields (entries 3 and 4). The reaction rate of thiophenes **4** was slower than that of furans **2**. The reaction of thiophene (**4d**) with **1a** gave the monoallylated product **5e** in 53% yield along with a trace amount of the diallylated product **5f** (eq 6).



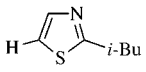
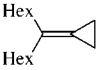
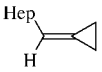
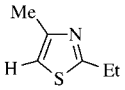
Addition of Thiazoles. The reaction to the 2-alkyl-substituted thiazoles **6** with **1** is summarized in Table 2 and eq 7. In the presence of 8 mol % $Pd(PPh_3)_4$, the



reaction of 2-isobutylthiazole (**6a**) with **1a** gave the corresponding allylated product **7a** in 77% yield (entry 1). Similarly, the reaction of **1b** with **6a** produced **7b** in 65% yield (entry 2). However, the reaction of **1c** with **6a** yielded **7c** in a lower yield (entry 3). Interestingly, **1** reacted with **6a** at the C-5 position regioselectively. The thiazole **6b** bearing a methyl group at the 4-position reacted with **1a** very sluggishly to give **7d** in a low yield (entry 4).

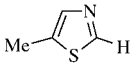
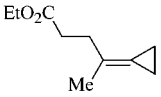
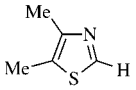
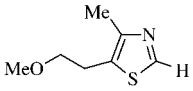
The 5-alkyl-substituted thiazoles **8** reacted with **1** at the C-2 position, giving the corresponding product **9** in

Table 2. Addition of Thiophenes 6 to Alkylidenecyclopropanes 1[a]

entry	1	6	7	yield / %[b]
1	 **1a**	 **6a**	**7a**	77
2	 **1b**	**6a**	**7b**	65
3	 **1c**	**6a**	**7c**	19
4	**1a**	 **6b**	**7d**	20

[a] The reaction of **1** (0.5 mmol) with **6** (2.5 mmol) was carried out in the presence of 8 mol % $Pd(PPh_3)_4$ in THF (0.5 mL) at 120 °C. [b] Isolated yield based on **1**.

Table 3. Addition of Thiophenes 8 at the 2-Position to Alkylidenecyclopropanes 1[a]

entry	1	8	yield of **9** / %	yield of **10** /%
1	 **1a**	 **8a**	**9a**, 37	**10a**, 3
2	 **1d**	**8a**	**9b**, 46	**10b**, 9
3	**1a**	 **8b**	**9c**, 16	**10c**, 19
4	**1a**	 **8c**	**9d**, 25	**10d**, 11

[a] The reaction of **1** (0.5 mmol) with **8** (2.5 mmol) was carried out in the presence of 8 mol % $Pd(PPh_3)_4$ in THF (0.5 mL) at 120 °C. [b] Isolated yield based on **1**.

moderate yields (eq 8). The results are summarized in

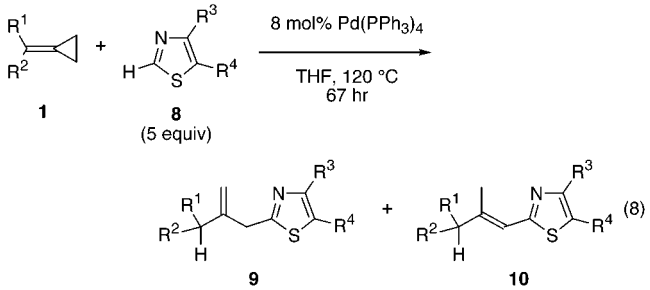
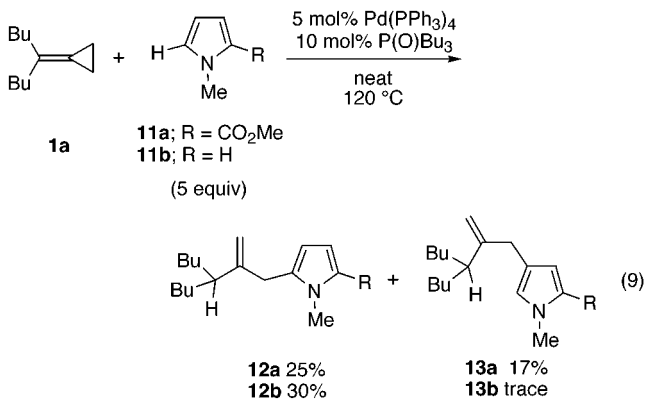


Table 3. The reaction of 5-methylthiazole (**8a**) with **1a** gave the corresponding adduct **9a** in 37% yield along with

a trace amount (3%) of the isomerized product **10a** (entry 1). The reaction of **1d** with **8a** afforded **9b** and **10b** in 46% and 9% yield, respectively (entry 2). The thiazole **8b** reacted with **1a**, producing **9c** and **10c** in 16% and 19% yield, respectively (entry 3). The reaction of the thiazole **8c** with **1a** gave a 2:1 mixture of **9d** and **10d** (entry 4).

Addition of Pyrroles. Furthermore, we utilized pyrroles **11** as a substrate for the palladium-catalyzed reaction with **1** (eq 9). Under the standard conditions,



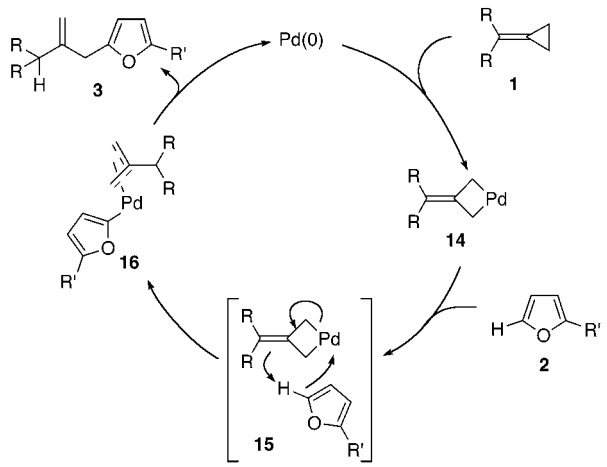
the reaction of methyl *N*-methylpyrrole-2-carboxylate **11a** with the alkylidenecyclopropane **1a** gave the α-allylated product **12a** in 25% yield along with the *β*-allylated product **13a** in 17% yield (eq 9). On the other hand, in the reaction of *N*-methylpyrrole **11b**, the α-allylated product **12b** was afforded selectively in 30% yield.

Discussion

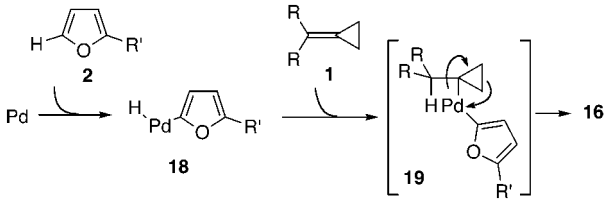
The catalytic addition of the α-C−H bond of heteroaromatics to a carbon−carbon multiple bond has rarely been investigated. The C−H bond addition of furans and thiophene to alkynes with $Rh_4(CO)_{12}$ catalyst has been reported.[18a] However, this reaction required a large excess of furans, significantly high CO pressures, and very high reaction temperatures. Quite recently, Fujiwara et al. reported the palladium-catalyzed addition of pyrroles and furans to alkynoates.[19] We found that the use of tributylphosphine oxide as a ligand accelerated the palladium-catalyzed addition of furans, thiophenes, and other heteroaromatics to alkylidenecyclopropanes. While an actual role of phosphine oxide is not clear, this ligand perhaps promotes the generation of coordinatively unsaturated palladium species, because of its labile characteristics in comparison with PPh_3.[20]

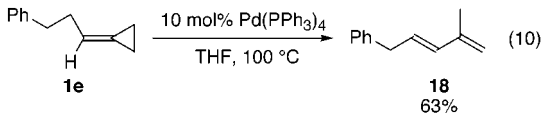
A plausible mechanism for the palladium-catalyzed addition of furans **2** with alkylidenecyclopropanes **1** is shown in Scheme 1. The oxidative addition of a distal bond of **1** to palladium(0) would lead to formation of palladacyclobutane **14**.[21] Since palladacyclobutane **14** is a sort of *σ*-allylpalladium species, a palladaene-type reaction with **2** would take place (**15**), giving the *π*-allylpalladium species **16**. Reductive elimination of palladium(0) would give the product **3**. The result of a labeling experiment using **2b**-*d* supports the proposed mechanism. Furthermore, we found that, in the presence of $Pd(PPh_3)_4$, cleavage of a distal bond of alkylidenecyclopropane **1e** occurred in THF, producing the diene **17** (eq 10). This fact clearly indicates that oxidative addition of a distal bond of an alkylidenecyclopropane to palladium takes place.

Scheme 1



Scheme 2





Alternatively, it is possible to explain this reaction by the hydropalladation mechanism shown in Scheme 2. Oxidative addition of palladium(0) to a carbon−hydrogen bond at the α-position of **2** would give hydridopalladium species **18**. Hydropalladation of **18** to the double bond of alkylidenecyclopropanes **1** followed by cleavage of a distal bond (as shown in **19**) would lead to the *π*-allylpalladium complex **16**. However, the hydropalladation mechanism is not likely because the reactivity of a carbon−hydrogen bond at the α-position of heteroaromatics is much lower than that of typical pronucleophiles.[22] In addition, we tried the palladium-catalyzed hydrofurylation on diphenylacetylene instead of alkylidenecyclopropanes. However, no adducts were obtained, and the starting substrates were recovered, suggesting the hydropalladation mechanism (Scheme 2) seems to be not operative.

The results clearly indicate the following order of reactivity of heteroaromatics: furan > thiophene ≈ thiazole (5-postion) > thiazole (2-position) ≈ *N*-methylpyrrole. Except for the lower reactivity of pyrroles, this order resembles that for the reactivity of the electrophilic

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reaction on heteroaromatic rings.[23] Addition of pyrroles at the β-proton is also seen in the electrophilic substitution. Perhaps, strong coordination of an electron-rich heteroaromatic ring to the palladacyclobutane complex **14** is the key to activate a C−H bond on the heteroaromatics. The lower reactivity of *N*-methylpyrroles may be due to the steric effect of a methyl group on the nitrogen carbon. The steric effect of a neighboring group was also seen in the reaction of 2-ethyl-4-methylthiazole (**6b**), giving the corresponding 5-allylated product **7d** in a low yield (Table 2, entry 4).

Conclusion

We are now in a position to carry out the allylation of heteroaromatics at the α-position of a heteroatom by the reaction between **1** and heteroaromatics in the presence of Pd catalyst. The formation of the highly strained intermediate **14** may be the key to activate a much less reactive C−H bond at the α-position of heteroaromatics. The allylation of heteroaromatics at the α-position is feasible by using the carboanion reaction of heteroaromatics with allyl halides.[24] However, the present methodology does not produce metal salts as a byproduct, which are inevitably afforded in the traditional carbanion reactions.

Experimental Section

General Procedures. Furans, thiophenes, thiazoles, and pyrroles were purchased. All alkylidenecyclopropanes were prepared following the reported procedure.[11c]

General Procedure of the Addition of the Furan Derivatives 2 to the Methylenecyclopropanes 1. To a mixture of $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) and tributylphosphine oxide (10.9 mg, 0.05 mmol) were added the furan derivatives **2** (2.5 mmol) and the alkylidenecyclopropanes **1** (0.5 mmol) under an Ar atmosphere in a pressure vial. After being heated at 120 °C for 15−37 h, the reaction mixture was filtered through a short florisil column using ethyl acetate as an eluent. Separation by passing through a florisil column (hexane as an eluent) and purification by middle-pressure liquid column chromatography (silica gel) using hexane as an eluent afforded the allylation products **3**.

Data for 2-(3-Butyl-2-methyleneheptyl)-5-methylfuran (3a): IR (neat) 3103−2858, 1643, 1618, 1568, 1465, 1458, 1220, 1020, 893, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 6.9 Hz, 6H), 1.09−1.37 (m, 12H), 2.01 (m, 1H), 2.24 (s, 3H), 3.25 (s, 2H), 4.76 (m, 1H), 4.79 (m, 1H), 5.85 (m, 1H), 5.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.55, 14.09, 22.85, 29.58, 32.49, 33.61, 45.74, 105.89, 107.15, 111.58, 149.33, 150.55, 152.02; HRMS (EI) calcd for $C_{17}H_{28}O$ *m/z* 248.2139, found *m/z* 248.2147.

Data for Ethyl 5-(3-Butyl-2-methyleneheptyl)thiophenecarboxylate (5a): IR (neat) 3076−2858, 1714, 1643, 1539, 1456, 1367, 1280, 1267, 1091, 896, 817, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 7.0 Hz, 6H), 1.07−1.42 (m, 15H), 2.05 (m, 1H), 3.45 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.79 (m, 1H), 4.87 (m, 1H), 6.81 (d, J = 3.8 Hz, 1H), 7.69 (d, J = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07, 14.36, 22.81, 29.53, 33.45, 34.34, 45.71, 60.92, 112.48, 126.76, 131.86, 133.39, 150.44, 151.02, 162.65; HRMS (EI) calcd for $C_{19}H_{30}O_2S$ *m/z* 264.1974, found *m/z* 322.1965.

Data for 5-(3-Butyl-2-methyleneheptyl)-2-(2-methylpropyl)thiazole (7a): IR (neat) 3170−2732, 1687, 1643, 1465, 1155, 1051, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.9 Hz, 6H), 0.98 (d, J = 6.0 Hz, 6H), 1.31 (m, 13H), 2.07 (m, 1H), 2.82 (d, J = 7.4 Hz, 2H), 3.39 (s, 2H), 4.78 (s, 1H), 4.82 (s, 1H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.96, 22.16, 22.72, 29.51, 29.69, 31.07, 33.51, 42.29, 45.52, 112.02, 136.40, 139.85, 150.61, 169.61; HRMS (EI) calcd for $C_{19}H_{33}NS$ *m/z* 307.2332, found *m/z* 307.2335.

Data for 2-(3-Butyl-2-methyleneheptyl)-5-methylthiazole (9a): IR (neat) 3103−2858, 1637, 1604, 1458, 1448, 1377, 1116, 1093, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.9 Hz, 6H), 1.12−1.42 (m, 12H), 2.04 (m, 1H), 2.42 (s, 3H), 3.56 (s, 2H), 4.86 (d, J = 11.3 Hz, 1H), 7.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.97, 14.03, 22.79, 29.47, 29.86, 33.34, 37.62, 45.83, 112.96, 139.66, 149.53, 167.95; HRMS (EI) calcd for $C_{16}H_{27}NS$ *m/z* 265.1863, found *m/z* 265.1885.

Data for 2-(3-Butyl-2-methyl-1-heptenyl)-5-methylthiazole (10a): IR (neat) 3076−2856, 1746, 1648, 1635, 1547, 1457, 1401, 1379, 1298, 1117, 1045, 1009, 913 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 7.1 Hz, 6H), 1.19−1.41 (m, 12H), 1.94 (s, 3H), 2.05 (m, 1H), 2.46 (s, 3H), 6.49 (s, 1H), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.85, 14.03, 14.88, 22.79, 29.45, 29.72, 33.87, 50.61, 112.41, 141.39, 149.28,165.89; HRMS (EI) calcd for $C_{16}H_{27}NS$ *m/z* 265.1863, found *m/z* 265.1843.

Data for Methyl 5-(3-Butyl-2-methyleneheptyl)-1-methylpyrrole-2-carboxylate (12a): IR (neat) 2954−2858, 1705, 1643, 1485, 1463, 1434, 1382, 1253, 1218, 1188, 1107, 896, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 7.5 Hz, 6H), 1.19−1.41 (m, 12H), 2.05 (m, 1H), 3.21 (s, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.39 (s, 1H), 4.80 (s, 1H), 5.95 (d, J = 4.0 Hz, 1H), 6.92 (J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10, 22.82, 29.65, 30.92, 32.39, 33.51, 45.92, 50.83, 109.02, 111.62, 117.29, 121.99, 138.53, 149.01, 161.86; HRMS (EI) calcd for $C_{19}H_{31}NO_2$ *m/z* 305.2353, found *m/z* 305.2375.

Data for Methyl 4-(3-Butyl-2-methyleneheptyl)-1-methylpyrrole-2-carboxylate (13a): IR (neat) 2954−2856, 1708, 1648, 1485, 1432, 1421, 1375, 1342, 1257, 1189, 1104, 896, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 7.0 Hz, 6H), 1.15−1.37 (m, 12H), 2.05 (m, 1H), 3.02 (s, 2H), 3.79 (s, 3H), 3.88 (s, 3H), 4.68 (s, 1H), 4.74 (s, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.15, 22.85, 29.64, 30.58, 33.64, 36.55, 45.85, 50.89, 110.63, 118.50, 121.16, 128.61, 133.76, 152.05, 161.78; HRMS (EI) calcd for $C_{19}H_{31}NO_2$ *m/z* 305.2353, found *m/z* 305.2343.

Supporting Information Available: Experimental information including characterization data of all products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0255126

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