Direct Preparation of 3-Thienyl Organometallic Reagents: 3-Thienylzinc and 3-Thienylmagnesium Iodides and 3-Thienylmanganese Bromides and Their Coupling Reactions

Reuben D. Rieke,* Seung-Hoi Kim, and Xiaoming Wu

Department of Chemistry, University of Nebraska−Lincoln, Lincoln, Nebraska 68588-0304

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3-Thienylzinc and 3-thienylmagnesium iodides can be generated from the direct oxidative addition of Rieke zinc and magnesium to 3-iodothiophene, respectively. The direct preparation of 3-thienylmanganese bromides from the reaction of Rieke manganese with 3-bromothiophene and 3,4-dibromothiophene is also performed. These 3-thienyl organometallic reagents have been found to be regiostable intermediates and undergo coupling reactions with a variety of versatile electrophiles such as acid chlorides, aryl iodides, aldehydes, and disulfide.

Introduction

3-Substituted thiophene derivatives have been utilized for the preparation of useful compounds in both materials and pharmaceutical science. For instance, poly(3-alkylthiophene) films have potential for good processability[1] and have been found to be stable for extended periods under a number of conditions.[2] The properties of these polymers are strongly dependent upon the substutents of the thiophene ring. More interestingly, 3-substituted thiophene derivatives have been found to be topical carbonic anhydrase inhibitors.[3] Consequently, the development of synthetic methodology for 3-substituted thiophene derivatives has attracted much attention.

To date, the most widely used methods for the preparation of 3-substituted thiophene derivatives are the coupling reactions of 3-thienyl organometallic reagents with electrophiles. The intermediates used in these reactions are generally obtained via either a metal−halogen exchange reaction of 3-bromothiophene with *n*-butyllithium[4] or the metathesis of the 3-lithiothiophene with different metal halides.[5]

The reaction of electrophiles with 3-lithiothiophene reagents has been widely used since it was introduced by Gronowitz.[4] However, the utility of these reactions is limited owing to the lack of regiospecificity as well as decomposition of the thiophene ring at room temperature.[4b,6] For instance, 3-lithiothiophene was demonstrated to have a temperature-dependent stability in polar etheral solvents and slowly underwent 2- and 3-regioexchange as well as decomposition at temperatures higher than −25 °C. To obviate this problem, direct preparation of 3-thienyl organometallic reagents has been developed.

The formation of novel organometallic compounds by the reaction of organic substrates with finely divided metal powders (active metals) represents a powerful tool for the synthetic chemist.[7] Highly reactive metal, Rieke metals (M*),[8] generated from the reduction of metal salts with lithium using naphthalene or biphenyl as an electron carrier in THF, have been used to synthesize a variety of organometallic reagents under mild conditions, and the resulting organometallic reagents undergo coupling reaction with versatile electrophiles to afford carbon−carbon bond-forming products.

For example, in 1973, we reported a new method for the preparation of a highly active zinc metal.[9] This reactive zinc underwent oxidative addition to aryl and alkyl halides to give rise to the corresponding organozinc reagents. The preparation of highly reactive manganese metal and its application for the oxidative addition to carbon−halogen bonds was also reported in 1996 from our laboratory.[10]

These discoveries prompted us to investigate whether we could apply these findings to 3-halothiophenes which are unreactive toward directive oxidative addition of a transition metal to afford 3-thienyl organometallic reagents. Suprisingly, there have been no direct synthetic methods to generate 3-thienyl organometallic reagents. More recently, direct preparation of 3-thienylzinc bromide using a simple electrochemical method was reported.[11]

The direct oxidative addition of Rieke zinc (Zn*) and Rieke magnesium (Mg*) to 3-iodothiophene was com-

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(1) (a) Jen, K.-Y.; Miller, G. G.; Elsenbaumer, R. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1346−1347. (b) Hotta, S.; Gughooputh, S. D. D. V.; Heeger, A. J.; Wudl, F. *Macromolecules* **1987**, *20*, 212−215. (c) Sato, M.; Tanaka, S.; Kaeriyama, K. *J. Chem. Soc., Chem. Commun.* **1986**, 873−874.

(2) (a) Waltman, R. J.; Diaz, A. F.; Bargon, J. *J. Electrochem. Soc.* **1984**, *131*, 1452. (b) Waltman, R. J.; Bargon, J. *Can. J. Chem.* **1986**, *64*, 76.

(3) (a) Hartman, G. D.; Halczenko, W.; Smith, R. L.; Sugrue, M. F.; Mallogra, P. J.; Michelson, S. R.; Randall, W. C.; Schwam, H.; Sondey, J. M. *J. Med. Chem.* **1992**, *35*, 3822−3831. (b) Holmes, J. M.; Lee, G. C. M.; Wijino, M.; Weinkam, R.; Wheeler, L. A.; Garst, M. E. *J. Med. Chem.* **1994**, *37*, 1646−1651.

(4) (a) Gronowitz, S.; Hakansson, R. *Arkiv. Kemi.* **1959**, *17*, 73−82. (b) Gronowitz, S. In *Organic Sulphur Chemistry-Structure, Mechanism, and Synthesis*; Sterling, C. J. M., Ed.; Butterworths: London, 1975; pp 203−228.

(5) (a) Zhang, Y.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 435−444. (b) Ritter, S. K.; Noftle, R. E. *Chem. Mater.* **1992**, *4*, 872−879. (c) Arnswald, M.; Neumann, W. P. *J. Org. Chem.* **1993**, *58*, 7022−7028. (d) Jaysuriya, N.; Kagan, J. *Heterocycles* **1986**, *24*, 2261−2264. (e) Yamamura, K.; Miyake, H.; Nakatsuji, S. *Chem. Lett.* **1992**, 1213−1216. (f) Gronowitz, S. *Arkiv. Kemi.* **1958**, *12*, 533−545.

(6) (a) Ritter, S. K.; Noftle, R. E. *Chem. Mater.* **1992**, *4*, 872. (b) Frohlich, H.; Kalt, W. *J. Org. Chem.* **1990**, *55*, 2993. (c) Gronowitz, S. *Adv. Heterocycl. Chem.* **1963**, *1*, 75.

(7) Reviews about active metals: (a) Rieke, R. D. *Science* **1989**, *24*, 1260−1264. (b) Furstner, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *92*, 164−189 and references cited therein.

(8) (a) Zhu, L.; Wehmeyer, M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445−1453. (b) Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1989**, *54*, 3247−3252. (c) Rochfort, G. L.; Rieke, R. D. *Inorg. Chem.* **1986**, *25*, 348−355. (d) Rieke, R. D. *Top Curr. Chem.* **1975**, *59*, 1 (e) Rieke, R. D.; Wehmeyer, R. M.; Wu, T.-C.; Ebert, G. W. *Tetrahedron* **1989**, *45*, 443−454.

(9) Rieke, R, D.; Hudnall, P. M.; Uhm, S. *J. Chem. Soc., Chem. Commun.* **1973**, 269.

(10) Kim, S. H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197−2200.

(11) Gosmin, C.; Nedlec, J. Y.; Perichon, J. *Tetrahedron Lett.* **1997**, *38*, 1941−1942.

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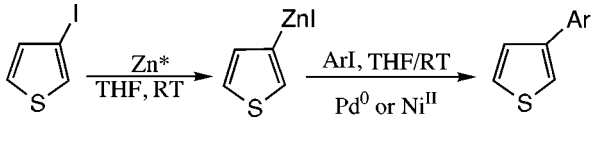
Scheme 1. Preparation of 3-Thienylzinc Iodide and Its Coupling Reaction



1 **2** **3a-f**

97 - 100% 40 - 80%

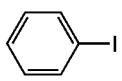
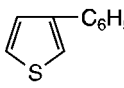
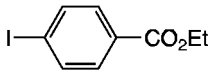
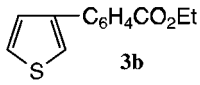
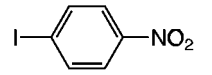
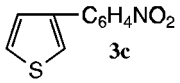
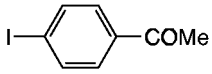
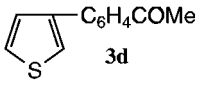
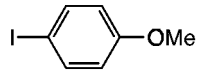
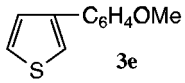
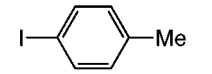
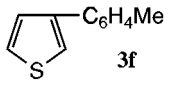
pleted under mild conditions in high yields, and the coupling reactions of the resulting 3-thienylzinc and 3-thienylmagnesium iodides with electrophiles were performed.[12] Not only commercial Mg but also Zn* and Mg* are unreactive toward 3-bromothiophene. Unfortunately, our first attempt at synthesizing either 3-thienylzinc or 3-thienylmagnesium bromide by the oxidative addition of Zn* and Mg* to 3-bromothiophene failed, even though Mg* and Zn* can readily undergo oxidative addition to 2-bromothiophene or other aromatic heterocyclic halides.[13] However, use of Rieke manganese (Mn*) gave 3-thienylmanganese bromide. The coupling reaction products were also obtained when 3-thienylmanganese bromide was reacted with various electrophiles.[14] It is interesting to note that this methodology can be applied to 3,4-dibromothiophene in the preparation of symmetrical and/or unsymmetrical 3,4-disubstituted thiophene derivatives.

Result and Discussion

The Rieke metals, Zn* and Mg*, are generally prepared via the reduction of $ZnCl_2$ and $MgCl_2$ by Li using naphthalene as an electron carrier in THF as mentioned above.[7] The active metals can be washed using THF to remove both the electron carrier and the lithium chloride. These Rieke metals readily undergo oxidative addition to 3-iodothiophene[15] to form 3-thienyl organometallic reagents which react with electrophiles in THF at room temperature. The same method can be applied to the preparation of Rieke manganese (Mn*). Reduction of manganese halides (MnI_2, $MnBr_2$, and $MnCl_2$) by Li using naphthalene as an electron carrier in THF affords a slurry of Mn* at room temperature. The resulting Mn*, however, is partially soluble in THF. Due to this, no washing was performed to remove naphthalene and other salts and the Mn* was used as a slurry. The preparation of the active metals and the subsequent reactions of the organometallic reagents are conducted under an argon atmosphere.

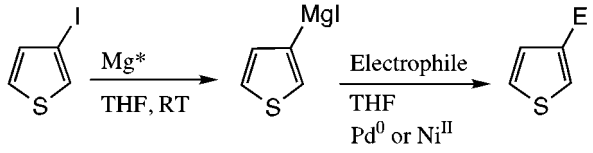
Preparation of 3-Thienylzinc Iodide and Its Coupling Reactions. As shown in Scheme 1, 3-thienylzinc iodide was generated by the reaction of 3-iodothiophene with Rieke zinc (Zn*). 3-Iodothiophene reacted slightly exothermically with Zn* (2 equiv) immediately upon addition. The conversion of 3-iodothiophene to 3-thienylzinc iodide was completed at room temperature in 8−10 h according to GC analysis. There was no sign of homocoupling. The resulting 3-thienylzinc iodide underwent cross-coupling reactions with a (Scheme 1) wide range of aromatic halides in the presence of a catalytic amount of Ni(dppe)Cl_2 or Pd(PPh_3)$_4$ generating functionalized and nonfunctionalized 3-arylthiophenes in moderate to good yields (Table 1). The reactivity of the organozinc species was found to be substrate dependent. The halides with an electron-withdrawing group in the para position (Table 1, entries 2−4) were more reactive than the halides with an electron-donating group in the para position (Table 1, entries 6 and 7).

Table 1. Coupling Reactions of 3-Thienylzinc Iodide

Entry	Aryliodides	Catalysts[a]	Product[b]	Yield (%)[c]
1		A	 **3a**	80
2		A	 **3b**	80
3		B	 **3c**	68
4		B	 **3d**	62
6		B	 **3e**	45
7		A	 **3f**	40

[a] **A**: Ni(dppe)Cl_2, **B**: Pd(PPh_3)$_4$). [b] All products have been fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS, or elemental analysis. [c] Isolated yield.

Scheme 2. Preparation of 3-Thienylmagnesium Iodide and Its Coupling Reaction



1 **4** **5a-d**

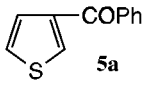
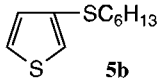
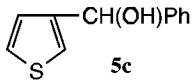
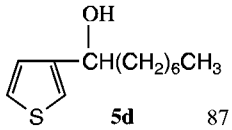
97 - 100% 33 - 87%

3-Thienylmagnesium iodide was also readily prepared from the oxidative addition of Mg* to 3-iodothiophene. Generally, 97−100% of 3-iodothiophene was converted to 3-thienylmagnesium iodide in 5−7 h using 1.5 equiv of Mg*. Once again, there was no sign of homocoupling. The 3-thienyl Grignard reagent reacted with different electrophiles such as aldehydes and acid chlorides as well as alkyl disulfides to afford 3-substituted thiophenes (Scheme 2).

Table 2 contains some representative results for the reactions of 3-thienylmagnesium iodide with electrophiles. When the 3-thienylmagnesium iodide was treated with benzoyl chloride at −30 °C, the corresponding

(12) Wu, X.; Rieke, R. D. *J. Org. Chem.* **1995**, *60*, 6658−6659.
(13) (a) Chen, T.; Rieke, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 10087−10088. (b) Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 5373−5374. (c) Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron Lett.* **1993**, *34*, 5955-5956.
(14) Kim, S. H.; Rieke, R. D. *Tetrahedron Lett.* **1997**, *38*, 993−996.
(15) 3-Iodothiophene is easily prepared via iodination of room temperature stable 3-lithiothiophene using 1,2-diiodoethane at ambient temperature: Wu, X.; Chen. T.-A.; Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1994**, *35*, 3673−3674.

Table 2. Coupling Reactions of 3-Thienylmagnesium Iodide

Entry	Electrophile	Condition	Product[a]	Yield (%)[b]
1	PhCOCl	THF, -30 °C	 **5a**	77
2	$C_6H_{13}SSC_6H_{13}$	THF, RT	 **5b**	62
3	PhCOH	THF, RT	 **5c**	33
4	$CH_3(CH_2)_6COH$	THF, RT	 **5d**	87

[a] All products have been fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS, or elemental analysis. [b] Isolated yield.

ketone (**5a**) resulted in a 77% isolated yield (Table 2, entry 1). Similarly, entries 2−4 in Table 2 demonstrate reactions of 3-thienylmagnesium iodide with a disulfide and aldehydes.

Regiostability of 3-Thienyl Organometallic Reagents. As mentioned already, 3-lithiothiophene in THF is temperature sensitive and converts to 2-lithiothiophene at temperatures above −25 °C.[4b,6] Therefore, the regiostability of the 3-thienylzinc iodide and -magnesium iodide, prepared by exothermic oxidative addition in THF at room temperature, was also questionable. In order to clarify the room temperature regiostability of 3-thienylmagnesium iodide, we compared the NMR data of the products of the reaction of 3-thienyl magnesium iodide with $C_6H_{13}SSC_6H_{13}$ at ambient temperature and 2-lithiothiophene with $C_6H_{13}SSC_6H_{13}$ at −30 °C to room temperature. The NMR data of the products obtained in these coupling reactions are summarized in Scheme 3.

Comparison of the ^{1}H and ^{13}C NMR data of 3-(hexylthio)thiophene (**5b**), prepared from 3-thienylmagnesium iodide, shows no 2-(hexylthio)thiophene (**8**), which was prepared from 2-lithiophene. In fact, no detectable amount of **8** was found either in the NMR spectra of compound **5b** or in the GC spectra of crude and purified compound **5b**.

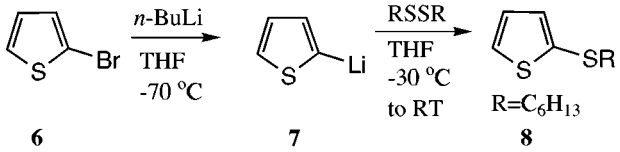
From this information, it can be concluded that 3-thienylmagnesium iodide is a regiostable intermediate at room temperature in THF[16] and maintains regiostability during coupling.

Similarly, it was observed that 3-thienylzinc iodide was also regiostable at ambient temperature in THF. As indicated by the NMR data below, the chemical shifts of the two compounds are identical (see ref 17).

Preparation of 3-Thienylmanganese Bromide and (4-Bromo-3-thienyl)manganese Bromide and Their Reactions. 3-Thienylmanganese bromide[18] was easily prepared from the reaction of 2 equiv of Rieke manganese (Mn*) with 3-bromothiophene (1 equiv). The oxidative addition of Mn* to 3-bromothiophene giving 3-thienylmanganese bromide was accomplished in THF at room temperature overnight. The regiostabilty of 3-thienylmanganese bromide was investigated by comparing NMR data of one of the final products. In order to do this, benzoyl chloride was chosen as the electrophile and the product was compared with that obtained from 3-thienylmagnesium iodide. The two products (**5a** and **5a′**) had chemical shifts which were identical within experimental error.[19] Therefore, it can be concluded that 3-thienylmanganese bromide is also a regiostable reagent at room temperature. It is also shown that (3-bromo-4-thienyl-)manganese bromide can be achieved as the major product from the reaction of 1 equiv of 3,4-dibromothiophene and 2 equiv of Mn* (Scheme 4).[20] This procedure was completed at room temperature in 5 h. A suggested mechanism presented in Scheme 4 was supported by the analysis of the final products which were obtained from the consecutive cross-coupling reactions with acid chlorides and aryl iodides. According to the high-resolution mass spectra of **11d** in Table 3 and **11g**, **11h**, and **11i** in Table 4, the second bromine atom is still retained in the final products.

The reactions of 3-thienylmanganese bromide with acid chlorides gave the corresponding ketones in moderate to high yields. In these reactions, the steric nature of the

Scheme 3



6 **7** **8**

^{13}C NMR Chemical Shift and the Assigment for **5b** and **8** Thiophene Ring

	C_2	C_3	C_4	C_5
5b	122.6	132.3	129.6	126.0
8	135.0	133.1	127.4	128.8

^{1}H NMR Chemical Shift and the Assigment for **5b** and **8** Thiophene Ring

	H_2	H_3	H_4	H_5
5b	7.11(dd)	-	7.02(dd)	7.31(dd)
8	-	7.11(dd)	6.97(dd)	7.32(dd)

(16) Although 3-thienylmagnesium bromide was prepared via metathesis of 3-lithiophene with magnesium bromide in ethyl ether as described in refs 5d−f, the room temperature regiostability of the Grignard reagent was not discussed.

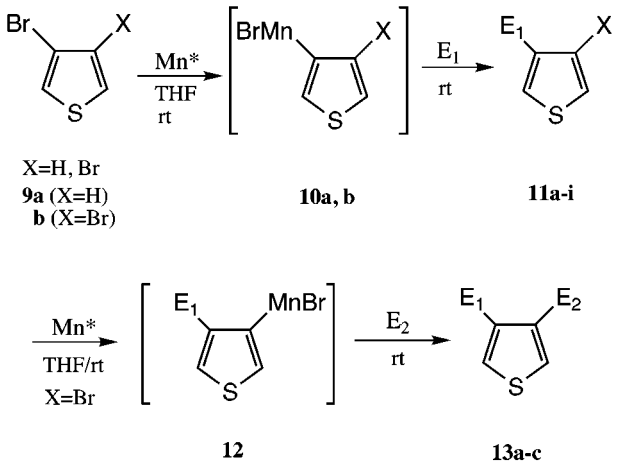
(17) Compound 3-phenylthiophene (**3a**): ^{13}C NMR δ 142.4, 135.9, 128.8, 127.1, 126.4, 126.3, 126.2, 120.3. 3-Phenylthiophene prepared from the reaction of 3-bromothiophene with phenylmagnesiun bromide: ^{13}C NMR δ 142.3, 135.8, 128.8, 127.1, 126.4, 126.3, 126.2, 120.2. See: Chen, T.-A. Ph.D. Dissertation, University of Nebraska−Lincoln, 1994, p 52.

(18) (a) For a general review of organomanganese reagents, see: Normant, J. F.; Cahiez, G. *Modern Synthetic Methods*; John Wiley & Sons Inc.: Chichester, 1983, Vol. 3, pp 172−216 and references cited therein.

(19) Chemical shifts for 3-benzoylthiophene (**5a′**), prepared from the reaction of 3-thienylmanganese bromide with benzoyl chloride: ^{13}C NMR δ 189.91, 141.19, 138.52, 133.84, 132.23, 129.27, 128.50, 128.28, 126.13. For **5a**: see Experimental Section.

(20) The formation of bis-organomanganese bromides cannot be ruled out on the basis our gas chromatography monitoring. After acidic quenching of the reaction mixture followed by gas chromatography analysis, less than 5% of thiophene was detected.

Scheme 4. Preparation of 3-Thienylmanganese Bromides and Their Coupling Reactions



acid chloride was found to have a significant effect on the coupling reaction. High yields (91% and 73%) were obtained from using 3-bromo- and 4-bromobenzoyl chloride as an electrophile, respectively (Table 3). In contrast to these results, the coupling reaction with 2-bromobenzoyl chloride gave lower yield due to the steric effect of the α-bromine of benzoyl chloride (Table 3, entry 1).

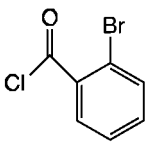
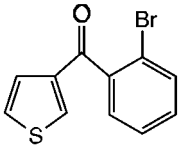
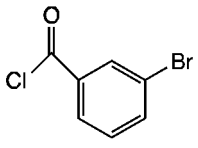
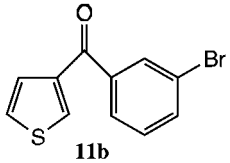
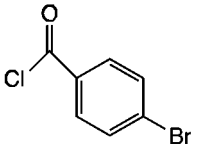
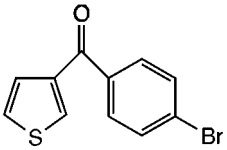
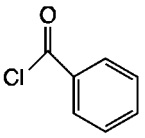
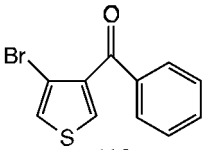
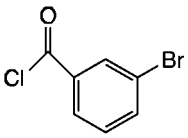
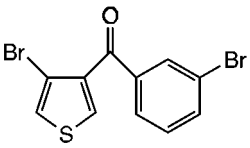
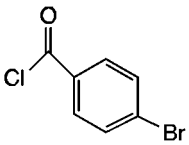
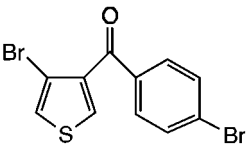
The coupling reaction of (3-bromo-4-thienyl)manganese bromides with acid chlorides gives the corresponding ketones in good isolated yields (Table 3, entries 4−6). No transition metal catalysts are required to complete the coupling reaction.

Coupling reactions with aryl iodides were also examined. These reactions were run with a catalytic amount of $Pd(PPh_3)_4$ catalyst and gave the corresponding C−C bond-forming products in good yields (Table 4, entries 4−6) under mild reaction conditions (room temperature, 30 min). The results of this reaction are summarized in Table 4. However, in the presence of a catalytic amount of [1,2-bis(diphenylphosphine)ethane]nickel(II) chloride, $Ni(dppe)Cl_2$, the reaction afforded the homocoupling product of 3-thienylmanganese bromide, 3-(3′-thienyl)-thiophene, in 44−58% isolated yields. From these reaction conditions, no cross-coupling product was obtained. It is noteworthy that the two steps, consecutive oxidative addition and subsequent cross-coupling, can be completed at room temperature in a few hours.

As shown in Scheme 4, the same strategy was applied to 4-substituted 3-bromothiophenes to make unsymmetrical 3,4-disubstituted thiophenes.

Table 5 represents the cross-coupling products obtained showing moderate yields (36−66%). Almost the same reaction conditions used in the reaction of 3-bromothiophene were also applied to complete this step. Oxidative addition of Mn* to the 3-substituted 4-bromothiophenes was performed at room temperature in 5 h, and the subsequent coupling reactions of the resulting thienylmanganese bromides with benzoyl chlorides afforded unsymmetrical 3,4-disubstituted thiophenes (Table 5, entries 1 and 2). The coupling reaction with benzoyl chloride was completed at room temperature in 30 min in the absence of a catalyst. Pd(0)-catalyzed C−C bond formation was also achieved from the reaction of the 3-substituted 4-thienylmanganese bromide. When the (3-phenyl-4-thienyl)manganese bromide was treated with ethyl 4-iodobenzoate in the presence of $Pd(PPh_3)_4$, ethyl 4-(3-phenyl-4-thienyl)benzoate (**13c**) was obtained (Table 5, entry 3).

Table 3. Coupling Reactions of 3-Thienylmanganese Bromides with Acid Chlorides

Entry	Thiophene	Electrophile	Product [a]	Yield (%)[b]
1	**9a**		 **11a**	34
2	**9a**		 **11b**	91
3	**9a**		 **11c**	79
4	**9b**		 **11d**	80
5	**9b**		 **11e**	83
6	**9b**		 **11f**	62

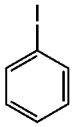
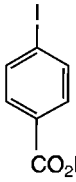
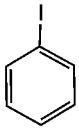
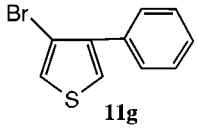
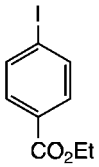
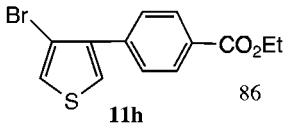
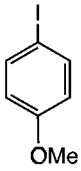
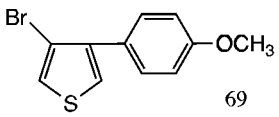
[a] All products have been fully characterized by ^1H NMR, ^{13}C NMR, HRMS, or elemental analysis. [b] Isolated yield (based on electrophile).

Summary and Conclusions

In conclusion, a simple but efficient procedure for preparing 3-thienylzinc and 3-thienylmagnesium iodides and 3-thienylmanganese bromides via the direct oxidative addition of Rieke zinc, Rieke magnesium, and Rieke manganese, respectively, has been demonstrated. These organometallics are regiostable in THF at room temperature as indicated by NMR studies. From a synthetic point of view, these results are significant, in that these 3-thienyl organometallic reagents can be used as important intermediates in the synthesis of 3-substituted thiophene derivatives. The resulting 3-thienyl organometallic reagents undergo coupling reaction with acid chlorides to give the corresponding ketones, and in the presence of a catalyst, carbon−carbon bond-forming products were obtained in moderate to good yields.

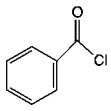
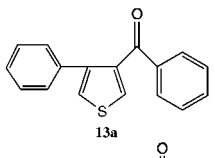
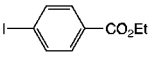
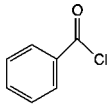
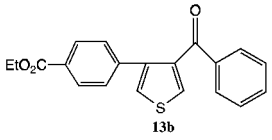
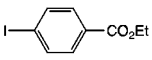
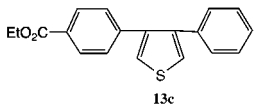
It is also important to note that both steps, oxidative addition of Mn* and the following cross-coupling reaction of organomanganese reagents, are performed under mild conditions. More significantly, symmetrically and/or

Table 4. Pd-catalyzed Coupling Reaction of 3-Thienylmanganese Bromides[a]

Entry	Thiophene	Electrophile(E_1)	Product [b]	Yield (%)[c]
1	**9a**		**3a**	61
2	**9a**		**3b**	70
3	**9b**		 **11g**	65
4	**9b**		 **11h**	86
5	**9b**		 **11i**	69

[a] 10 mol % $Pd(PPh_3)_4$ was used as a catalyst (based on electrophile). [b] All products have been fully characterized by ^1H NMR, ^{13}C NMR, HRMS, or elemental analysis. [b] Isolated yield (based on electrophile).

Table 5. Preparation of Unsymmetrical 3,4-Disubstituted Thiophenes

Entry	E_1	E_2	Product [a]	Yield (%)[b]
1			 **13a**	66
2			 **13b**	46
3			 **13c**	36[c]

[a] All products have been fully characterized by ^1H NMR, ^{13}C NMR, HRMS, or elemental analysis. [b] Isolated yield (based on electrophile). [c] 10 mol % $Pd(PPh_3)_4$ was used as a catalyst (based on electrophile).

unsymmetrically 3,4-disubstituted thiophene derivatives can be obtained via consecutive reactions of 3,4-dibromothiophene.

Experimental Section

General Methods. ^1H NMR (300 MHz) spectra were recorded in $CDCl_3$ solutions. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Fully decoupled ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ solutions. The center peak of $CDCl_3$ (77.0 ppm) was used as the internal reference. FTIR spectra are reported as cm^{-1}. Mass spectra were performed by the Nebraska Center for Mass Spectrometry at the University of Nebraska—Lincoln. Elemental analyses were performed by Desert Analytics (Tucson, AZ).

All manipulations were carried out under an atmosphere of argon on a dual manifold vacuum/argon system. The Linde prepurified grade argon was further purified by passage over a BASF R3−11 catalyst column at 150 °C, a phosphorus pentoxide column, and a column of granular potassium hydroxide. Lithium, naphthalene, and metal halides were weighed out and charged into reaction flasks under in a Vacuum Atmospheres Company drybox. Tetrahydrofuran was distilled immediately before use from Na/K alloy under an atmosphere of argon.

Gas chromatrographic analyses were done on a Hewlett-Packard 5890A chromatograph using a stainless steel column (12 ft × $^1/_8$ in.) packed with GP 10% SP 2100 on a 100/120 Supelcoport. Analytical thin-layer chromatography was performed using Merck 5735 indicating plates precoated with silica gel 60 F254 (layer thickness 0.2 mm). The product spots were visualized with either iodine or a solution of vanillin. Preparative thin-layer chromatographic separations were obtained using Analtech silical gel GF (layer thickness 2 mm) preparative plates. Liquid chromatographic purifications were performed by flash column chromatography using glass columns packed with Merck silica gel 60 (230−400 mesh). Low-temperature conditions were obtained by utilizing dry ice/acetone baths.

Preparation of Highly Reactive Magnesium (Mg*). Highly reactive magnesium was prepared by the reduction of anhydrous magnesium chloride with lithium using naphthalene as an electron carrier. In a typical preparation, lithium (9.68 mmol), naphthalene (1.48 mmol), and anhydrous magnesium chloride (4.71 mmol) were *vigorously* stirred in freshly distilled THF (15 mL) for 3.5 h at room temperature. After the addition of 10 mL of THF, the newly formed magnesium slurry (black powder) was allowed to settle for 2 h, and the supernatant was drawn off via cannula, leaving 4 mL of solvent covering the Mg*. Freshly distilled THF was added (10 mL). (Note: The number of millimoles of Mg* cited in this paper refers to the theoretical amount possible, based on the original amount of anhydrous magnesium chloride.)

Preparation of Highly Active Zinc. Active zinc was prepared by the reduction of anhydrous zinc chloride ($ZnCl_2$) with lithium using naphthalene as an electron carrier. In a representative preparation, $ZnCl_2$ (10 mmol) in THF (10 mL) was transferred dropwise via cannula to lithium (20 mmol) and naphthalene (2 mmol) in stirring THF (5 mL). The stirring was stopped when the lithium was totally consumed, and the active zinc powder was allowed to settle for 0.5 h. The supernatant was then removed via cannula, and fresh distilled THF (10 mL) was added. The slurry was briefly stirred and then allowed to settle down for 0.5 h again, and the supernatant was subsequently removed. Freshly distilled THF (15 mL) was added to newly formed and washed Zn* which was ready for oxidative addition.

Preparation of Highly Active Manganese (Mn*). To the mixture of lithium (20 mmol), naphthalene (2 mmol), and 10 mmol of manganese halides (chloride, bromide, and iodide) was added via syringe freshly distilled THF at room temperature, and then the resulting mixture was allowed to stir at room temperature for 1−3 h. A black slurry was obtained and ready for use.

Preparation of 3-Thienylzinc Iodide and 3-Arylthiophenes: A Typical Synthesis of 3-Thienylbenzenes 3a−f. 3-Iodothiophene (5 mmol) was added via syringe to active zinc (10 mmol) being stirred in THF (15 mL) at room temperature. The slurry was stirred at room temperature for 8−10 h. The reaction was monitored by gas chromatography. After completion of the oxidative addition, the mixture was allowed to stand so that the excess Zn* powder could settle out of the solution. Since the newly prepared 3-thienylzinc iodide was

dissolved in THF, the supernatant was then transferred to a mixture of aryl iodide (4 mmol) and Ni(dppe)Cl_2 (0.4 mol %) with stirring in THF (5 mL) at room temperature. 3-Thienylbenzene (**3a**) was obtained in 80% isolated yield based upon 3-iodothiophene. Other arylthiophenes were prepared in a similar way using either Ni(dppe)Cl_2 or Pd(PPh_3)$_4$ as catalyst in 40−80% isolated yields.

3-Thienylbenzene (3a): ^{1}H NMR δ 7.69−7.66 (m, 2H), 7.51−7.42 (m, 5H), 7.39−7.36 (m, 1H); ^{13}C NMR δ 142.36, 135.86, 128.78, 127.10, 126.44, 126.32, 126.16, 120.25; HRMS calcd for $C_{10}H_8S$ 160.0347, found 160.0343. Anal. Calcd for $C_{10}H_8S$: C, 74.96; H, 5.03; S, 20.01. Found: C, 74.99; H, 4.92; S, 19.88.

Ethyl *p*-(3-thienyl)benzoate (3b): ^{1}H NMR δ 8.10−8.07 (m, 2H), 7.68−7.65 (m, 2H), 7.57−7.56 (m, 1H), 7.44−7.42 (m, 2H), 4.42 (q, J = 7.25 Hz, 2H), 1.42 (t, J = 6.85 Hz, 3H) ^{13}C NMR δ 166.34, 141.22, 139.89, 130.12, 128.98, 126.59, 126.14, 126.11, 121.77; HRMS calcd for $C_{13}H_{12}O_2S$ 232.0558, found 232.0554. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21; O, 13.77; S, 13.80. Found: C, 67.16; H, 5.07; O, 13.74; S, 13.45.

***p*-(3-Thienyl)nitrobenzene (3c):** ^{1}H NMR δ 8.27−8.24 (m, 2H), 7.75−7.72 (m, 2H), 7.64−7.63 (m, 1H), 7.48−7.43 (m, 2H); ^{13}C NMR δ 146.63, 141.88, 139.92, 127.27, 126.79, 126.00, 124.26, 123.17; HRMS calcd for $C_{10}H_7NO_2S$ 205.0197, found 205.0190; Anal. Calcd for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82; O, 15.59; S, 15.62. Found: C, 58.39; H, 3.25; N, 6.65; O, 15.64; S, 15.24.

***p*-(3-Thienyl)acetophenone (3d):** ^{1}H NMR δ 8.01−7.98 (m, 2H), 7.70−7.67 (m, 2H), 7.59−7.57 (m, 1H), 7.44−7.43 (m, 2H), 2.62 (s, 3H); ^{13}C NMR δ 197.48, 141.06, 140.17, 135.64, 129.03, 126.73, 126.34, 126.14, 122.00, 26.54; HRMS calcd for $C_{12}H_{10}OS$ 202.0450, found 202.0450. Anal. Calcd for $C_{12}H_{10}OS$: C, 71.26; H, 4.98. Found: C, 71.01; H, 4.98.

***p*-(3-Thienyl)anisole (3e):** ^{1}H NMR δ 7.55−7.52 (m, 2H), 7.36−7.35 (m, 3H), 6.96−6.93 (m, 2H), 3.85 (s, 3H); ^{13}C NMR δ 158.90, 142.01, 128.76, 126.24, 126.03, 118.92, 114.19, 55.34; HRMS calcd for $C_{11}H_{10}OS$ 190.0452, found 190.0457. Anal. Calcd for $C_{11}H_{10}OS$: C, 69.22; H, 5.21; O, 8.41; S, 13.80. Found: C, 69.25; H, 5.15; O, 8.60; S, 16.75.

***p*-(3-Thienyl)toluene (3f):** ^{1}H NMR δ 7.52−7.50 (m, 2H), 7.43−7.39 (m, 3H), 7.26−7.21 (m, 2H), 2.40 (s, 3H); ^{13}C NMR δ 142.36, 136.82, 133.12, 129.46, 126.32, 126.31, 125.99, 21.07; HRMS calcd for $C_{11}H_{10}S$ 175.0502, found 174.0503.

Preparation of 3-Thienylmagnesium Iodide and 3-Substituted Thiophenes 5a−d. 3-Iodothiophene (5 mmol) was added to the washed Mg* (7.5 mmol) in THF (15 mL) with stirring at room temperature. The slurry was stirred for 5−7 h at room temperature. After completion of oxidative addition, the excess active magnesium was allowed to settle out of the organomagnesium solution. The supernatant was cannulated to different electrophiles (4 mmol) in THF (10 mL) at different temperatures. After the mixture was stirred, the reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with diethyl ether (20 mL × 2). The combined organic layers were washed with brine (20 mL × 2), dried over anhydrous $MgSO_4$, and concentrated using a rotary evaporator. Flash column chromatography (ethyl acetate/hexanes) afforded 3-substituted thiophenes **5a−d** in 33−87% isolated yields.

3-Benzoylthiophene (5a): ^{1}H NMR 7.93−7.92 (m, 1H), 7.86−7.83 (m, 2H), 7.61−7.55 (m, 2H), 7.50−7.45 (m, 2H), 7.39−7.36 (m, 1H); ^{13}C NMR δ 189.88, 141.18, 138.52, 133.83, 132.20, 129.26, 128.49, 128.27, 126.12; HRMS calcd for $C_{11}H_8OS$ 188.0296, found 188.0291.

3-(Hexylthio)thiophene (5b): ^{1}H NMR δ 7.33−7.30 (m, 1H), 7.11−7.10 (m, 1H), 7.02−7.00 (m, 1H), 2.83 (t, J = 7.17 Hz, 2H), 1.61 (q, J = 7.17 Hz, 2H), 1.45−1.26 (m, 6H), 0.88 (t, J = 6.59 Hz, 3H); ^{13}C NMR δ 132.34, 129.64, 125.98, 122.85. Anal. Calcd for $C_{10}H_{16}S_2$: C, 59.95; H, 7.99; S, 32.00. Found: C, 59.86; H, 8.30; S, 32.37.

1-Phenyl-1-(3-thienyl)methanol (5c): ^{1}H NMR δ 7.42−7.26 (m, 6H), 7.19−7.18 (m, 1H), 7.01−6.99 (m, 1H), 5.88 (s, 1H), 2.34 (s, 1H); ^{13}C NMR δ 145.26, 143.31, 128.46, 127.71, 126.44, 126.35, 126.14, 121.61, 72.75; HRMS calcd for $C_{11}H_{10}OS$ 190.0452, found 190.0444.

1-Heptyl-1-(3-thienyl)methanol (5d): ^{1}H NMR δ 7.30−7.28 (m, 1H), 7.17−7.16 (m, 1H), 7.08−7.06 (m, 1H), 4.74 (t, J = 6.68 Hz, 1H), 2.00 (s, 1H), 1.79−1.25 (m, 12H), 0.88 (t, J = 7.16, 3H); ^{13}C NMR δ 146.42, 125.94, 125.62, 120.56, 70.61, 38.35, 31.75, 29.40, 29.17, 25.65, 22.58, 14.02.

Preparation of 2-(Hexylthio)thiophene (8): ^{1}H NMR δ 7.33−7.31 (m, 1H), 7.11−7.10 (m, 1H), 6.98−6.95 (m, 1H), 2.83 (t, J = 7.17 Hz, 2H), 1.62−1.61 (m, 2H), 1.42−1.31 (m, 6H), 0.91 (t, J = 6.58 Hz, 3H); ^{13}C NMR δ 134.97, 133.14, 128.80, 38.93, 31.30, 29.31, 28.05, 22.48, 13.98; HRMS calcd for $C_{10}H_{16}S_2$ 200.0693, found 200.0690.

Typical Procedure for the Preparation of 3-Thienylmanganese Bromides and Their Coupling Reactions with Acid Chlorides (Scheme 4). To a slurry of Rieke manganese (10.0 mmol) in THF (10 mL) under argon was added 3,4-dibromothiophene (5.0 mmol) at room temperature, and the mixture was stirred at room temperature for 5 h. 1,2-Dibromoethane[21] (6.0 mmol) was added neat to the reaction mixture at 0 °C, and the mixture was allowed to warm to room temperature over 20 min. To the resulting organomanganese reagent was added acid chloride (3.0 mmol) neat at room temperature via syringe. The resulting mixture was sitrred at room temperature for 30 min. The mixture was quenched with 3 M HCl (10 mL) and extracted with ether (2 x 10 mL), and the combined organic layers were sequentially washed with saturated $NaHCO_3$, $Na_2S_2O_3$ and NaCl solutions, dried over $MgSO_4$, and concentrated. Flash chromatography (ethyl acetate/hexanes) afforded the corresponding ketones in 34−91% isolated yield.

3-(2-Bromobenzoyl)thiophene (11a): ^{1}H NMR δ 7.80 (dd, J = 2.86, 2.86 Hz, 1H), 7.65 (dd, J = 7.87, 7.63 Hz, 1H), 7.57 (dd, J = 5.01, 5.25, 1H), 7.41−7.31 (m, 4H); ^{13}C NMR δ 189.18, 142.40, 141.11, 136.00, 135.91, 133.28, 131.14, 128.59, 127.59, 127.06, 126.70, 119.22; HRMS calcd for $C_{11}H_7BrOS$ 266.0490, found 265.9401.

3-(3-Bromobenzoyl)thiophene (11b): ^{1}H NMR δ 7.96−7.92 (m, 2H), 7.76−7.68 (m, 2H), 7.57 (dd, J = 5.01, 5.01 Hz, 1H), 7.46−7.33 (m, 2H); ^{13}C NMR δ 188.22, 140.67, 140.39, 135.16, 134.22, 132.11, 129.93, 128.39, 127.79, 126.51, 122.59; HRMS calcd for $C_{11}H_7BrOS$ 266.0490 found,

3-(4-Bromobenzoyl)thiophene (11c): ^{1}H NMR δ 7.92−7.91 (m, 1H), 7.74−7.71 (m, 2H), 7.66−7.62 (m, 2H), 7.59 (ddd, J = 5.01, 5.00, 5.25 Hz, 1H), 7.41−7.39 (m, 1H); ^{13}C NMR δ 188.84, 140.89, 137.31, 133.96, 133.87, 131.69, 130.89, 128.47, 127.32, 126.48; HRMS calcd for $C_{11}H_7BrOS$ 266.0490, found 265.9401.

3-Bromo-4-benzoylthiophene (11d): ^{1}H NMR δ 7.88−7.84 (m, 2H), 7.68−7.58 (m, 2H), 7.51−7.46 (m, 2H), 7.38 (d, J = 3.34 Hz, 1H); ^{13}C NMR 189.79, 139.21, 137.44, 133.25, 132.26, 130.05, 128.46, 125.08, 110.56; HRMS calcd for $C_{11}H_7BrOS$ 266.0490, found 265.9401.

3-Bromo-4-(3-bromobenzoyl)thiophene (11e): ^{1}H NMR δ 7.97−7.96 (m, 1H), 7.77−7.68 (m, 3H), 7.40−7.33 (m, 2H); ^{13}C NMR δ 188.16, 139.21, 138.56, 136.03, 132.85, 132.81, 132.75, 132.65, 130.03, 128.52, 125.43, 122.70, 110.46; HRMS calcd for $C_{11}H_{16}Br_2OS$ 343.8506, found 343.8508; EIMS *m/z* (relative intensity) 347.84 (31), 346.85 (7), 345.84 (62), 343.85 (30), 190.89 (98), 188.90 (100), 184.94 (26), 182.94 (25).

3-Bromo-4-(4-bromobenzoyl)thiophene (11f): ^{1}H NMR δ 7.72−7.59 (m, 5H), 7.39 (d, J = 3.57 Hz, 1H); ^{13}C NMR δ 188.67, 138.79, 136.09, 132.33, 132.29, 131.75, 131.40, 128.46, 125.30, 110.35; EIMS *m/z* (relative intensity) 348.80 (33), 345.80 (M^+, 14), 344.80 (43), 190.85 (99), 188.85 (100), 184.80 (41).

Typical Procedure for Pd-Catalyzed Coupling Reaction of 3-Thienylmanganese Bromides with Aryl Iodide (11g−i). 3-Thienylmanganese bromides were prepared as before. After being stirred, the mixture was allowed to cool down and 1,2-dibromoethane (3.01 mmol) was syringed neat at 0 °C. Then the mixture was gradually warmed to room temperature over 20 min. The resulting 3-thienylmanganese bromide was added via cannula to a mixture of ethyl 4-iodo-

(21) 1,2-Dibromoethane was used to consume the remaining active manganese in the reaction mixture because Mn* was active to additional electrophile to give a homocoupling product.

benzoate (1.88 mmol) and $Pd(PPh_3)_4$ (0.13 mmol) catalyst in THF at room temperature over 40 min. The mixture was stirred at room temperature for 2 h. An aqueous solution of HCl (3 M, 10 mL) was added, and the mixture was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed sequentially with $NaHCO_3$ (saturated 2 × 20 mL), $Na_2S_2O_3$ (saturated 2 × 20 mL), and NaCl (saturated 2 × 20 mL) and then dried over $MgSO_4$. Removal of solvents and flash chromatography (ethyl acetate/hexanes) afforded ethyl 4-(3-thienyl)benzoate (**3b**) in 70% isolated yield.

3-Bromo-4-phenylthiophene (11g): ^{1}H NMR δ 7.55−7.38 (m, 6H), 7.28 (d, J = 3.58 Hz, 1H); ^{13}C NMR δ 141.98, 135.11, 128.98, 128.17, 127.75, 124.02, 123.38, 123.35, 111.04; HRMS calcd for $C_{10}H_7BrS$ 238.0490, found 237.9452.

Ethyl 4-(3-bromo-4-thienyl)benzoate (11h): ^{1}H NMR δ 8.10 (dd, J = 8.59, 5.00 Hz, 2H), 7.58 (dd, J = 8.50, 5.00 Hz, 2H), 7.40 (d, J = 3.50 Hz, 1H), 7.33 (d, J = 4.00 Hz, 1H), 4.40 (q, J = 7.50 Hz, 2H), 1.41 (t, J = 7.00 Hz, 3H); ^{13}C NMR δ 167.03, 140.17, 130.14, 129.60, 125.23, 124.96, 111.37, 61.70, 15.00; HRMS calcd for $C_{13}H_{11}BrO_2S$ 310.0770, found 309.9663.

3-Bromo-4-(4-methoxyphenyl)thiophene (11i): ^{1}H NMR δ 7.44 (dd, J = 8.59, 4.53 Hz, 2H), 7.35 (d, J = 3.33 Hz, 1H), 7.20 (d, J = 3.58 Hz, 1H), 6.97 (dd, J = 8.94, 4.47 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR δ 159.27, 141.67, 131.92, 130.16, 128.56, 128.40, 123.83, 122.59, 113.56, 111.30, 55.31; HRMS calcd for $C_{11}H_9BrOS$ 268.0660, found 267.9557.

Preparation of Unsymmetrical 3,4-Disubstituted Thiophenes 13a,b. Rieke manganese (Mn*) was prepared as before. To a slurry of Mn* (3.55 mmol) in THF was added **11i** (1.75 mmol) at room temperature, and then the mixture was stirred at that temperature for 3 h. After being stirred, the mixture was allowed to cool down and 1,2-dibromoethane (2.13 mmol) was syringed neat at 0 °C. Then the mixture was gradually warmed to room temperature over 20 min. Benzoyl chloride (1.33 mmol) was added neat via syringe. The mixture was stirred at room temperature for 30 min. An aqueous solution of HCl (3 M, 10 mL) was added, and the mixture was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed sequentially with $NaHCO_3$ (saturated, 2 × 20 mL), $Na_2S_2O_3$ (saturated, 2 × 20 mL), and NaCl (saturated 2 × 20 mL) and then dried over $MgSO_4$. 3-Benzoyl-4-phenylthiophene (**13a**) was isolated from the crude from silica gel chromatography (ethyl acetate/hexanes) in 66%: ^{1}H NMR δ 7.85−7.74 (m, 3H), 7.51−7.49 (m, 1H), 7.41−7.23 (m, 8H); ^{13}C NMR δ 191.89, 143.51, 139.96, 137.83, 135.46, 132.85, 132.32, 132.24, 129.94, 128.46, 128.20, 127.28, 124.03; HRMS calcd for $C_{17}H_{12}OS$ 264.0609, found 264.0604.

Ethyl 4-(3-benzoyl-4-thienyl)benzoate (13b): ^{1}H NMR δ 7.96−7.35 (m, 16H), 7.35 (q, J = 7.15 Hz, 2H), 4.35 (q, J = 7.15 Hz, 2H), 1.36 (t, J = 7.15 Hz, 3H); ^{13}C NMR δ 191.52, 166.31, 142.58, 139.97, 137.69, 133.10, 132.84, 129.94, 129.59, 129.23, 128.37, 125.10, 60.88, 14.25; HRMS calcd for $C_{20}H_{16}O_3S$ 336.0820, found 336.0820.

Preparation of Ethyl 4-(3-Phenyl-4-thienyl)benzoate (13c): 3-Substituted 4-thienylmanganese bromides (1.05 mmol) were prepared as before. After being stirred, the mixture was allowed to cool down and 1,2-dibromoethane (1.57 mmol) was syringed neat at 0 °C. Then the mixture was gradually warmed to room temperature over 20 min. The resulting 3-thienylmanganese bromide was added via cannula to a mixture of 4-iodobenzoate (1.00 mmol) and $Pd(PPh_3)_4$ (0.10 mmol) catalyst in THF at room temperature over 40 min. The mixture was stirred at room temperature for 20 min. An aqueous solution of HCl (3 M, 10 mL) was added, and the mixture was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed sequentially with $NaHCO_3$ (saturated, 2 × 20 mL), $Na_2S_2O_3$ (saturated, 2 × 20 mL), and NaCl (saturated 2 × 20 mL) and then dried over $MgSO_4$. Removal of solvents and flash chromatography (ethyl acetate/hexanes) afforded ethyl 4-(3-phenyl-4-thienyl)benzoate (**3c**) in 36% isolated yield: ^{1}H NMR δ 7.96−7.93 (m, 2H), 7.38 (dd, J = 20.74, 14.07 Hz, 2H), 7.28−7.16 (m, 7H), 4.37 (q, J = 7.16 Hz, 2H), 1.38 (t, J = 7.15 Hz, 3H); ^{13}C NMR δ 166.47, 141.73, 141.02, 140.70, 136.14, 129.48, 128.97, 128.84, 128.81, 128.27, 127.08, 124.97, 124.41, 60.88, 14.34; HRMS calcd for $C_{19}H_{16}O_2S$ 308.0871, found 308.0875.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compound **5d**, **11a**, **11c**, **11d**, **11f**, **11g**, **13a**, **13b**, and **13c** and HETCOR NMR spectra of compounds of **5b** and **8** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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