The First Regioselective Hydroformylation of Acetylenic Thiophenes Catalyzed by a Zwitterionic Rhodium Complex and Triphenyl Phosphite

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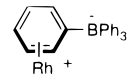
The hydroformylation of acetylenic thiophenes is readily accomplished by using the zwitterionic rhodium catalyst (η^6-$C_6H_5BPh_3$)$^-$Rh$^+$(1,5-COD) and triphenyl phosphite in the presence of CO and H_2. This catalytic system affords, as the major product, the α,β-unsaturated aldehyde with the aldehyde and thiophene attached to the same olefin carbon atom. Assistance of sulfur from the heterocycle provides excellent regioselectivity and yields when the acetylenic unit is a propargyl ether or ester, phenylacetylene, or an enyne.

Introduction

The coordinating ability of sulfur-containing compounds to reactive sites of metal complexes has long been a limiting factor toward the catalysis of sulfur-containing materials.[1] Catalysis in the presence of sulfur has been of considerable interest for many years due to applications in organic chemistry,[2] the pharmaceutical[3] and polymer[4] industries.

In past years, we have shown how catalysis may be used for the selective aerobic oxidation of sulfides,[5] carbonylation of thiazolidines,[6] and thiocarbonylation of propargylic alcohols, allenes, allylic alcohols, and enynes with thiols and carbon monoxide, affording unsaturated thioesters and dithioesters.[7] Hydroformylation of a variety of alkenes including vinyl sulfones and sulfoxides was readily catalyzed by the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)$^-$Rh$^+$(1,5-COD) (**1**).[8] To our knowledge, the hydroformylation of a triple bond to form an α,β-unsaturated aldehyde in the presence of sulfur has not been accomplished.



(1,5-COD)

1

New advances have been recently reported for the hydroformylation of internal acetylenes. Results obtained by Buchwald and co-workers in 1995,[9] and by Hidai and co-workers in 1997,[10] demonstrate that the hydroformylation of acetylenes can be readily accomplished in high regioselectivity and yields. Recently, we described the hydroformylation of conjugated enynes in which a catalytic system comprising the zwitterionic rhodium complex **1** and triphenyl phosphite were utilized with CO and H_2 to form α,β-unsaturated aldehydes in excellent regioselectivity and moderate to good yields.[11]

Acetylenic thiophenes and other acetylenic sulfur-containing heterocycles occur naturally in plants,[12] and may be readily prepared by the Pd/CuI coupling of haloheterocycles with terminal alkynes.[13] Over the past few years, increased attention has been given to sulfur-containing heterocycles which contain substituted unsaturated groups.[14] Hydroformylation of an acetylenic unit in these heterocycles would result in the formation of either a branched or linear α,β-unsaturated aldehyde with a thiophene conjugating unit. These novel materials would have the potential to be applied in further modifications to new functionalities, or transformations in-

(1) (a) Dubois, M. R. *Chem. Rev.* **1989**, *89*, 1. (b) Hegedus, L. L.; McCabe, R. W. In *Catalyst Poisoning*; Marcel Dekker: New York, 1984. (c) Hutton, A. T. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 1151.

(2) (a) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd ed.; Chapman and Hall: London, 1995. (b) Meyers, A. I. In *Heterocycles in Organic Chemistry*; Taylor, E. C., Weissberger, A., Eds.; John Wiley and Sons: New York, 1974. (c) Paquette, L. A. *Principles of Modern Heterocyclic Chemistry*, W. A. Benjamin Inc.: New York, 1968.

(3) (a) Krohn, K., Kirst, H. A., Maag, H., Eds. *Antibiotics and Antivirial Compounds*; VCH Publishers Inc.: New York, 1993. (b) Lednicer, D.; Mitscher, L. A. *Organic Chemistry of Drug Synthesis*; John Wiley and Sons: New York, 1977.

(4) (a) Choi, W.; Sanda, F.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 1189. (b) Ng, S. C.; Chan, H. S. O.; Wong, P. M. L.; Tan, K. L.; Tanb, B. T. G. *Polymer* **1998**, *39*, 4963. (c) Longridge, J. J.; Rawson, J. M. *Polyhedron* **1998**, *17*, 1871.

(5) Aldea, R.; Alper, H. *J. Org. Chem.* **1995**, *60*, 8365.

(6) Khumtaveeporn, K.; Alper, H. *J. Am. Chem. Soc.* **1994**, *116*, 5662.

(7) (a) Xiao, W.-J.; Alper, H. *J. Org. Chem.* **1997**, *62*, 3422. (b) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1998**, *63*, 2609. (c) Xiao, W.-J..; Alper, H. *J. Org. Chem.* **1998**, *63*, 7939. (d) Xiao, W.-J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1999**, *64*, 2080.

(8) (a) Totland, K.; Alper, H. *J. Org. Chem.* **1993**, *58*, 3326. (b) Alper, H.; Zhou, J. Q. *J. Org. Chem.* **1992**, *57*, 3729. (c) Amer, I.; Alper, H. *J. Am. Chem. Soc.* **1990**, *112*, 3674. (d) Lee, C. W.; Alper, H. *J. Org. Chem.* **1995**, *60*, 499.

(9) Johnson, J. R.; Cuny, G. D.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1760.

(10) Ishii, Y.; Miyashita, K.; Kamita, K.; Hidai, M. *J. Am. Chem. Soc.* **1997**, *119*, 6448.

(11) Van den Hoven, B. G.; Alper, H. *J. Org. Chem.* **1999**, *64*, 3964.

(12) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, 1996; Vol. 2, p 679.

(13) (a) Carpita, A.; Lezzi, A.; Rossi, R.; Marchetti, F.; Merlino, S. *Tetrahedron* **1985**, *41*, 621. (b) Rossi, R.; Carpita, A.; Lezzi, A. *Tetrahedron* **1984**, *40*, 2773. (c) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312. (d) Ames, D. E.; Bull, D.; Takundwa, C. *Synthesis* **1981**, 364. (e) D'Auria, M.; De Mico, A.; D'Onofrio, F.; Piancatelli, G. *J. Org. Chem.* **1987**, *52*, 5243.

(14) (a) Boivin, J.; Huppe, S.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 8735. (b) Degl'Innocenti, A.; Funicello, M.; Scafato, P.; Spagnolo, P. *Tetrahedron Lett.* **1997**, *38*, 2171. (c) Varney, M. D.; Romines, W. H.; Palmer, C. L. PCT Int. Appl. WO 9,640,674, 1996. (d) Tanaka, H.; Fukuzumi, K.; Togawa, T.; Banno, K.; Ushiro, T.; Morii, M.; Nakatani, T. PCT Int. Appl. WO 9,633,195, 1996. (e) Chan, M. F.; Raju, B. G.; Kois, A.; Verner, E. J.; Wu, C.; Castillo, R. S.; Yalamoori, V.; Balaji, V. N. US Patent 5,594,021, 1997. (f) Labadie, S. S. *Synth. Commun.* **1998**, *28*, 2531.

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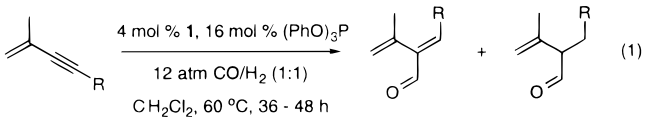
volving cyclization[15] or addition reactions,[16] ultimately assisting in the preparation of drugs[17] and pesticides.[18]

We now describe the use of catalytic quantities of **1**, in the presence of triphenyl phosphite, CO, and H_2, to attain the hydroformylation of both simple and functionalized acetylenic thiophenes in good to excellent conversions, selectivities, and yields.

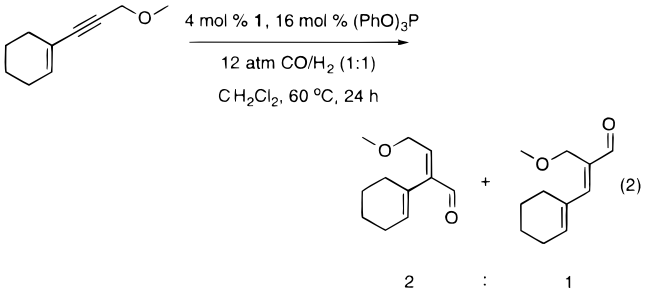
Results and Discussion

The hydroformylation of conjugated enynes was performed using the zwitterionic rhodium complex **1** and triphenyl phosphite, 3−6 mmols of enyne, and 12 atm of synthesis gas at 60 °C for 36−48 h (eq 1). Under these conditions branched formyl dienes were obtained in 50−55% yields.[11]



(1)

During this investigation an interesting substrate was examined to gain insight into the mechanism of the reaction. The hydroformylation of 1-(3-methoxyprop-1-ynyl)cyclohexene resulted in two formyl dienes with a branched-to-linear ratio of 2:1 (eq 2).



(2)

It was conceivable that a dual interaction between the catalyst and substrate could occur prior to hydroformylation (Figure 1). The strength of this initial interaction may govern the resulting regioselectivity.

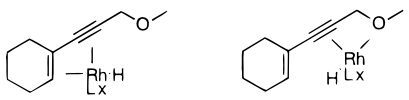


Figure 1. Rhodium coordination to an enyne prior to hydroformylation.

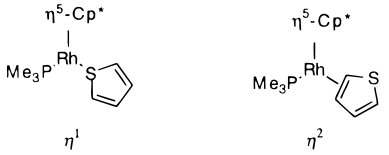
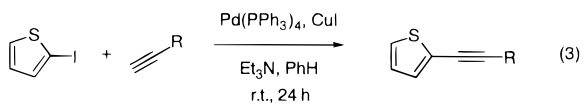


Figure 2. Thiophene coordination to a rhodium complex.

In 1997, a theoretical study on the binding of thiophenes to transition metals noted two possible modes of complexation to rhodium (Figure 2).[19] The η^1 complex (15 kcal/mol) was appreciably lower in binding energy than the η^2 complex (30 kcal/mol). This study suggested the possibility of a sulfur assisted hydroformylation of acetylenic thiophenes. In many studies,[20] including our own work on the hydroformylation of enynes, it was observed that when there is both a double bond and a triple bond present within a molecule, the triple bond is more reactive. This is consistent with the binding energy for rhodium−triple bond coordination being lower than the binding energy for the metal coordinating to a double bond. One could infer that the η^1 binding energy to the thiophene sulfur would be similar to that for a triple bond to rhodium. Having both of these functionalities adjacent to each other would result in a beneficial arrangement for the rhodium-catalyzed hydroformylation of the triple bond.

It was observed during our study on the hydroformylation of enynes that triphenyl phosphite is less active as a ligand than the functionalized bisphosphite ligand used by Buchwald and co-workers.[9] By controlling the substitution within the aromatic phosphite structure, the kinetics of the reaction can be readily controlled. It may be desirable in some cases to use a less active catalytic system to attain a product when the substrate is more active.

Acetylenic thiophenes may be readily prepared by the direct coupling of halo-substituted thiophenes (−Br and −I) with terminal alkynes in the presence of tetrakis-(triphenylphoshine)palladium, CuI, and base (eq 3).[13]



(3)

The acetylenic unit may have functionalities including alkyl, propargyl ether, alcohol, or ester, phenylacetylene, and enyne. Yields ranging from 65% to 90% were obtained in these reactions (Table 1).

(15) (a) Li, Y.; Thiemann, T.; Sawada, T.; Mataka, S.; Tashiro, M. *J. Org. Chem.* **1997**, *62*, 7926. (b) Katritzky, A. R.; Serdyuk, L.; Xie, L.; Ghiviriga, I. *J. Org. Chem.* **1997**, *62*, 6215. (c) Hoerndler, C.; Hansen, H. J. *Helv. Chim. Acta* **1997**, *80*, 2520. (d) Kaye, P. T.; Molema, W. E. *Chem. Commun.* **1998**, 2479. (e) Cossy, J.; Rakotoarisoa, H.; Kahn, P.; Desmurs, J.-R. *Tetrahedron Lett.* **1998**, *39*, 9671. (f) Jones, R. C. F.; Patel, P.; Hirst, S. C.; Smallridge, M. J. *Tetrahedron* **1998**, *54*, 6191. (g) Höppe, H. A., Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1545.

(16) (a) Boldi, A. M.; Johnson, C. R.; Eissa, H. O. *Tetrahedron Lett.* **1999**, *40*, 619. (b) Lu, T.-J.; Cheng, S.-M.; Sheu, L.-J. *J. Org. Chem.* **1998**, *63*, 2738. (c) Shiraishi, H.; Nishitani, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6234. (d) Yoshimatsu, M.; Oguri, K.; Ikeda, K.; Gotoh, S. *J. Org. Chem.* **1998**, *63*, 4475.

(17) (a) Chang, C.-T.; Chen, K.-M.; Liu, W.-H.; Lin, F.-I.; Wu, R.-T., U.S. Patent 5,602,170, 1997. (b) Chang, C.-T.; Chen, K.-M.; Liu, W.-H.; Lin, F.-I.; Wu, R.-T. U.S. Patent 5,747,525, 1998. (c) Ebermann, R.; Alth, G.; Kreitner, M.; Kubin, A. *J. Photochem. Photobiol., B* **1996**, *36*, 95. (d) Wierzbicky, M.; Sauveur, F.; Bonnet, J.; Tordjman, C. Fr. Demande FR 2,752,576, 1998. (e) Asari, T.; Okamoto, S.; Kono, S. Japanese Patent 10,316, 673, 1998.

(18) (a) Walter, H. PCT Int. Appl. WO 9,733,890, 1997. (b) Morita, K.; Murabayashi, A., Japanese Patent 09,095,482, 1997. (c) Kanehira, K.; Tagawa, H.; Shiono, M. Japanese Patent 09,104,682, 1997. (d) Fischer, R.; Dumas, J.; Bretschneider, T.; Gallenkamp, B.; Lieb, F.; Wernthaler, K.; Erdelen, C.; Wachendorff-Neumann, U.; Mencke, N.; Turberg, A. Ger. Offen DE 19,527,190, 1996. (e) Theobald, H.; Harries, V.; Kardorff, U.; Baeuerle, P.; Goetz, G. PCT Int. Appl. WO 9,314,079, 1993.

(19) Sargent, A. L.; Titus, E. P. *Organometallics* **1998**, *17*, 65.

(20) (a) Doyama, K.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* **1996**, *27*, 4497. (b) Doyama, K.; Joh, T.; Shiohara, T.; Takahashi, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4353. (c) Campi, E. M.; Jackson, W. R. *Aust. J. Chem.* **1989**, *42*, 471.

Table 1. Preparation of Acetylenic Thiophenes[a]

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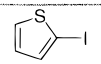
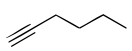
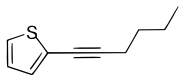
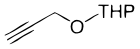
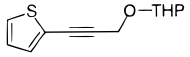
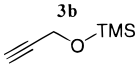
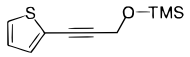
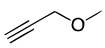
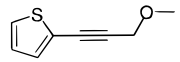
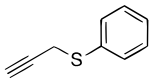
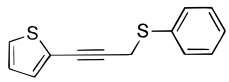
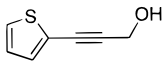
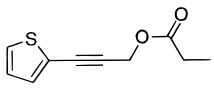
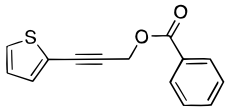
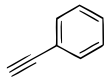
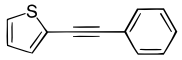
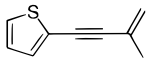
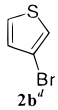
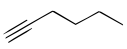
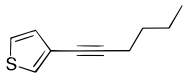
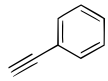
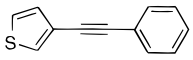
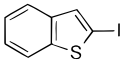
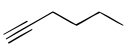
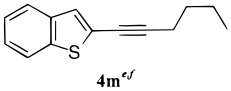
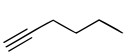
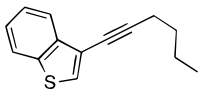
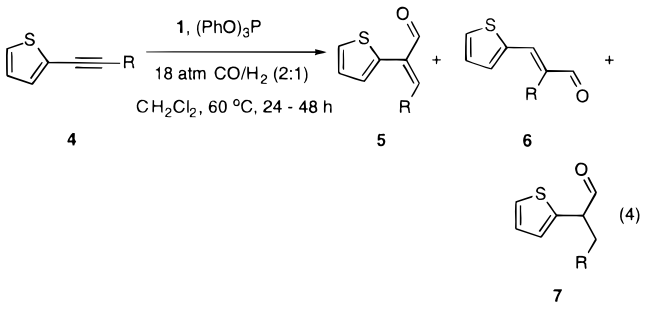
1	 **2a**	 **3a**	 **4a**	86
2		 **3b**	 **4b**	83
3		 **3c**	 **4c**	82
4		 **3d**	 **4d**	86
5		 **3e**	 **4e**	74
6		 **3f**	 **4f**	65
7		**3f**	 **4g**[c]	89
8		**3f**	 **4h**[c]	90
9		 **3g**	 **4i**	78
10		 **3h**	 **4j**	81
11	 **2b**[d]	 **3a**	 **4k**	79
12		 **3g**	 **4l**	75
13	 **2c**	 **3a**	 **4m**[e,f]	86
14	 **2d**	 **3a**	 **4n**[e,f]	85

[a] Reaction conditions: heterocycle (**2**), 20 mmol; alkyne (**3**), 25−30 mmol; $Pd(PPh_3)_4$, 0.2 mmol; CuI, 0.5 mmol; PhH, 50 mL; Et_3N, 15 mL; room temperature, 24 h. [b] The product was isolated by Kugelrohr distillation. [c] The ester was prepared by esterification of **4f**, and isolated by silica gel column chromatography using pentane/ether (90:10). [d] CH_2Cl_2 instead of PhH, reflux, 5 days. [e] Reflux. [f] The product was isolated via preparative HPLC size exclusion chromatography using $CHCl_3$ as the eluant.

In principle, the hydroformylation of acetylenic thiophenes could afford the isomeric unsaturated aldehydes **5** and **6** (eq 4).

Our initial investigation of thiophenynes utilized the same conditions employed for the hydroformylation of enynes. Using 3 mmol of 2-(hex-1-ynyl)thiophene (**4a**), 4 mol % **1**, 16 mol % $(PhO)_3P$, 10 mL of CH_2Cl_2, 6 atm of CO, and 6 atm of H_2 at 60 °C for 48 h resulted in only 70% conversion of **5a** accompanied by a dark red discoloration of the reaction mixture. Increasing the solvent



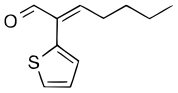
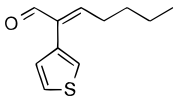
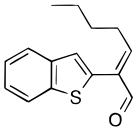
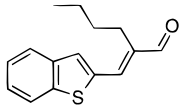
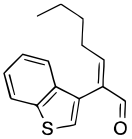
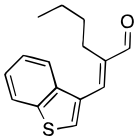
volume to 20 mL of CH_2Cl_2 resulted in the reaction proceeding to completion. The reaction mixture was yellow, and a substantial amount of **7**, R = *n*-C_4H_9, was formed here. The amount of the latter was reduced to less than 10% of the total yield by increasing the CO-to-H_2 ratio to 2:1. It was also necessary to increase the total pressure to 18 atm to enable the reaction to be complete after 48 h. When functionalized alkynylthiophenes were used as reactants, less catalyst and shorter reaction times were required to obtain complete conversion. Acetylenic thiophenes containing propargyl ether or ester functionalities required 1.5 mol % **1**, 6 mol % $(PhO)_3P$, and a reaction time of 24 h. Substrates having a double bond or phenyl groups were best hydroformylated with 2 mol % **1**, 8 mol % $(PhO)_3P$, and a reaction time of 24 h. The regioselectivity of the process is dependent, to some extent, on the catalyst loading. The higher the catalyst loading required, the greater the preference for **5**.

The hydroformylation of 2- and 3-substituted acetylenic alkylthiophenynes is completely regioselecive, affording **5** as the only product. For example, **5a** and **5k** were obtained from **4a** and **4k**, respectively, with <10% of **7** as a byproduct (Table 2, entries 1 and 2). Interestingly, the process becomes less selective using the corresponding benzothiophene reactants **4m** and **4n**. Hydroformylation of 2-(hex-1-ynyl)benzothiophene (**4m**) affords two aldehydes in 88% isolated yield, with the ratio of **5m** to **6m** being 5:1 (Table 2, entry 3). The hydroformylation of the isomeric 3-(hex-1-ynyl)benzothiophene (**4n**) also favored the branched aldehyde **5n**, but in a 64:21 ratio of **5n** to **6n** (Table 2, entry 4). The influence of the fused benzene ring may be explained by visualizing the approach of **1** toward the alkynylbenzothiophene (Figure 3). The freedom of rotation of the tetraphenylborate group bound to the rhodium complex (via π-complexation to one arene ring) is reduced when **1** is in close proximity to the 2-alkynylbenzothiophene. The freedom of rotation becomes even more constrained when **4n** is used as the substrate, thus affording **5n**/**6n** in a lower ratio than **5m**/**6m**.

Hydroformylation of propargyl ether or ester derivatives of acetylenic thiophenes affords two α,β-unsaturated aldehydes, the major product being **5** in all cases (Table 3). The ratio of **5** to **6** ranged from 2.5:1.0 to 3.3:1.0 (Table 3, entries 1−4), while acetylenic thiophene propargyl esters were obtained in a 1.8−2.3:1.0 ratio using **4g** and **4h** as substrates (Table 3, entries 5 and 6).

Good regioselectivity is also observed when the acetylenic unit has an aryl or vinyl group. The results for the hydroformylation of 2-(1-phenylacetylenyl)thiophene (**4i**) compared to 3-(1-phenylacetylenyl)thiophene (**4l**) (Table 4, entries 1 and 3) follow the same trend as that observed for 2- versus 3-alkynylbenzothiophenes (**4m** and **4n**), consistent with the proposed influence of the heterocyclic

Table 2. Hydroformylation of Derivatives Containing Alkyl Acetylenic Units[a]

Entry	4	Time (h)	Conv. (%)[b]	Product (Isolated Yield)[c,d]
1	**4a**	48	100	 (93)[e] **5a**
2	**4k**	48	100	 (90)[f] **5k**
3	**4m**	24	100	 (73) **5m**  (15) **6m**
4[g]	**4n**	48	100	 (64) **5n**  (21) **6n**

[a] Reaction conditions: **4**, 3 mmol; **1**, 0.12 mmol (4%), $(PhO)_3P$, 0.48 mmol (16%); CH_2Cl_2, 20 mL; CO, 12 atm; H_2, 6 atm; 60 °C. [b] The percent conversion was determined by ^1H NMR. [c] The ratio of **5** to **6** was determined by the ratio of their aldehyde ^1H NMR signals. [d] The products were isolated by silica gel column chromatography using a pentane:ether gradient ranging from 90:10 to 75:25 as eluant. [e] 7% of **7**, R = C_4H_9, was also formed. [f] 9% of the saturated aldehyde was formed as well. [g] The products were isolated by silica gel column chromatography using a pentane ether gradient ranging from 95:5 to 85:15 as eluant.

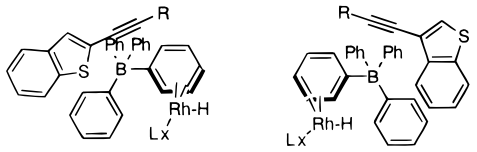


Figure 3. Approach of **1** to an alkynylbenzothiophene.

sulfur relative to the position of the triple bond. The further the sulfur atom is from the alkyne unit, the less its influence on the regioselectivity of the hydroformylation reaction. The 1-en-3-yne derivative **4j** affords a cyclopentenone (**8**) as the major product (Table 4, entry 2) possibly by intramolecular cyclization of the aldehyde **5j**. The minor product is the formyl diene **6j** which is in accord with our previous investigation of enynes.[11]

The above data demonstrate the influence of the heterocyclic sulfur atom on the hydroformylation process. Complex **9** may be generated for acetylenic thiophenes containing other functionalized groups. For reactants which also have ether and ester groups, a competing binding for rhodium is that of the alkyne and the functional units **10** (Figure 4). The preference for **5** relative to **6** may be due to a lower binding energy for **9** than for **10**. The coupled interaction with the lowest binding energy will become the major product, and the

Table 3. Hydroformylation of Thiophenynes Containing Propargyl Ether and Ester Units[a]

Entry	4	Conv. (%)[b]	Product (Isolated Yield)[c,d]	
1	**4b**	100	(69) **5b**	(25) **6b**
2	**4c**	100	(73) **5c**	(22) **6c**
3	**4d**	100	(70) **5d**	(27) **6d**
4[e]	**4e**	100	(73) **5e**	(23) **6e**
5[f]	**4g**	100	(57) **5g**	(31) **6g**
6[f]	**4h**	100	(63) **5h**	(30) **6h**

[a] Reaction conditions: **4**, 3 mmol; **1**, 0.045 mmol (1.5%), $(PhO)_3P$, 0.18 mmol (6%); CH_2Cl_2, 20 mL; CO, 12 atm; H_2, 6 atm; 60 °C, 24 h. [b] The percent conversion was determined by ^1H NMR. [c] The ratio of **5** to **6** was determined by the ratio of the aldehyde signals in the proton NMR. [d] The products were isolated by silica gel column chromatography using a pentane:ether gradient ranging from 90:10 to 75:25 as eluant. [e] **1**, 0.06 mmol; $(PhO)_3P$, 0.24 mmol. [f] The products were isolated by silica gel column chromatography using a pentane:ether gradient ranging from 90:10 to 50:50 as eluant.

higher binding energy interaction will result in attaining the minor product.

A possible mechanism for the heterocyclic sulfur directed hydroformylation of 2-alkynylthiophenes, shown in Figure 5, consists of the following steps: (1) the rhodium hydride **11** binds to the heterocycle, forming an η^1-sulfur-donor ligand complex (**12**); (2) the triple bond then coordinates to the metal (note, it is conceivable that complexation occurs in the opposite order); (3) intramolecular addition of the rhodium hydride to the triple bond of the alkynylthiophene can afford the (*E*)−isomer **15**; (4) CO insertion into **15** would give the acyl rhodium carbonyl species **16**; (5) reaction of the rhodium complex with hydrogen gives the α,β-unsaturated aldehyde **5**, and regenerates the hydride **11**.

Table 4. Hydroformylation of Acetylenic Thiophenes Containing Aryl or Vinyl Groups[a]

Entry	4	Conv (%)[b]	Product (Isolated Yield)[c,d]	
1	**4i**	100	(83) **5i**	(15) **6i**
2	**4j**	100	(48) **8**	(17) **6j**
3	**4l**	100	(58) **5l**	(30) **6l**

[a] Reaction conditions: **4**, 3 mmol; **1**, 0.06 mmol (2%), $(PhO)_3P$, 0.24 mmol (8%); CH_2Cl_2, 20 mL; CO, 12 atm; H_2, 6 atm; 60 °C, 24 h. [b] The percent conversion was determined by ^1H NMR. [c] The ratio of **5** to **6** was determined by the ratio of the aldehyde ^1H NMR signals. [d] The products were isolated by silica gel column chromatography using a pentane:ether gradient ranging from 90:10 to 75:25 as eluant.

9 **10**

Figure 4. Rhodium coordination prior to hydroformylation.

In conclusion, this study has demonstrated the significant influence of a thiophene sulfur on the regioselectivity of the hydroformylation of alkynes. Good, complete regioselectivity was observed in these reactions. This research has led to a greater understanding of the factors that influence the hydroformylation process. Some of the aldehydes formed are novel and have potential in both pharmaceutical and agrochemical businesses.

Experimental Section

Materials. 2-Iodothiophene, 3-bromothiophene, and all terminal alkynes were purchased from commercial sources. 2-Iodobenzothiophene,[21] 3-iodobenzothiophene,[21] and the zwitterionic rhodium complex $(\eta^6\text{-}C_6H_5BPh_3)^-Rh^+(1,5\text{-COD})$ (**1**)[22] were prepared according to the literature methods. All solvents were dried and distilled under N_2 prior to use.

General Procedure for the Pd/CuI Coupling of Iodothiophene to a Terminal Alkyne. To a 100 mL round−bottom flask purged with N_2 were added triethylamine (15 mL), the terminal alkyne **3** (25−30 mmol), PhH (50 mL), iodothiophene (**2**) (20 mmol), $Pd(PPh_3)_4$ (0.2 mmol), and CuI (0.5 mmol) at room temperature for 24 h. Methanol (10 mL) was added, the solvent was evaporated, and diethyl ether (200

(21) Gaeriner, R. *J. Am. Chem. Soc.* **1952**, *74*, 4950.
(22) Schrock, P. R.; Osborn, J. A. *Inorg. Chem.* **1970**, *9*, 2339.

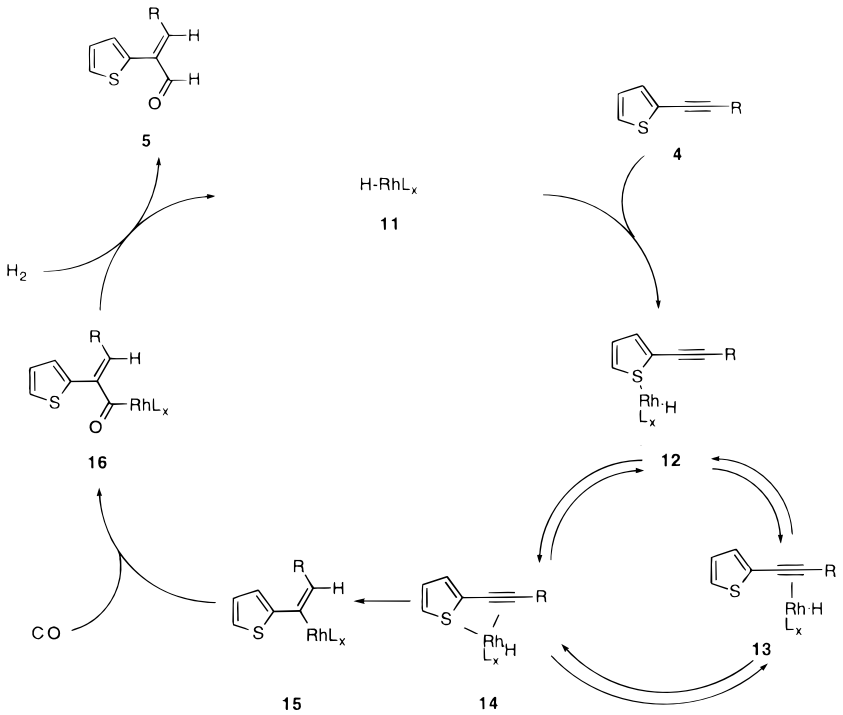


Figure 5. Proposed mechanism.

mL) was added to the resulting residue, leading to the precipitation of $Et_3NH^+I^-$. This mixture was filtered, washed with 10% HCl, distilled H_2O, and brine, and dried over anhydrous $MgSO_4$ or Na_2SO_4. The ether solution was decolorized with activated charcoal and evaporated and the resulting residue further purified by Kugelrohr distillation to give **4**.

2-(3-Hydroxyprop-1-ynyl)thiophene (4f): colorless liquid; IR ν(OH) 3332 cm^{-1}, ν(C≡C) 2222 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17−7.26 (m, 2H), 6.94 (dd, 1H, J = 6.0, 4.0 Hz). 4.48 (s, 2H), 2.19 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 133.0, 128.0, 127.6, 91.8, 79.6, 52.3; EI MS (*m*/*e*) 138 [M$^+$]; HRMS calcd for C_7H_6OS [M$^+$] 138.01394, found 138.01307.

General Procedure for the Preparation of Propargyl Ester Thiophene Derivatives. Triethylamine (2.8 mL, 20 mmol) was added dropwise to a stirred solution of 2-(3-hydroxyprop-1-ynyl)thiophene (**4f**) (1.38 g, 10 mmol), propionic or benzoic anhydride (12.5 mmol), and 0.12 g (1.0 mmol) of 4−(dimethylamino)pyridine in CH_2Cl_2 (40 mL). After 2 h the reaction mixture was treated with CH_2Cl_2 (60 mL), washed with 10% HCl, saturated $NaHCO_3$, and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation. The ester was further purified by silica gel chromatography using pentane/ether (90:10) as eluant.

2-(3-Propionoxyprop-1-ynyl)thiophene (4g): colorless liquid; IR ν(C≡C) 2230 cm^{-1}, ν(C═O) 1744; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20−7.27 (m, 2H), 6.94 (dd, 1H, J = 7.2, 2.4 Hz), 4.89 (s, 2H), 2.38 (q, 2H, J = 8.0 Hz), 1.15 (t, 3H, J = 7.7 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 174.3, 133.6, 128.4, 127.6, 122.6, 87.9, 80.3, 53.3, 28.0, 9.6; EI MS (*m*/*e*) 194 [M$^+$]; HRMS calcd for $C_{10}H_{10}O_2S$ [M$^+$] 194.04015, found 194.04172.

General Procedure for the Hydroformylation of Conjugated Thiophenynes. To a 45 mL autoclave containing a glass liner and stirring bar were added the zwitterionic rhodium complex **1** (0.045−0.12 mmol), triphenyl phosphite (0.18−0.48 mmol), the conjugated thiophenyne **4** (3 mmol), and CH_2Cl_2 (20 mL). The autoclave was flushed three times with carbon monoxide and pressurized to 12 atm, and then hydrogen was introduced to a total pressure of 18 atm. The autoclave was placed in an oil bath at 60 °C for 24−48 h, and then allowed to cool to room temperature. The autoclave was depressurized, the reaction mixture filtered through Celite, and the solvent removed by rotary evaporation. The resulting yellow residue was purified by silica gel chromatography using a pentane:ether gradient ranging from 90:10 to 75:25 as the eluant to afford products **5** and **6**.

Removal of any discoloration in **5** or **6**, caused by light or heat, was affected by preparative HPLC size exclusion chromatography using $CHCl_3$ as the eluant.

(*E*)-4-Propionoxy-2-(2-thienyl)-2-buten-1-al (5g): colorless liquid; IR ν_1(C═O) 1737 cm^{-1}, ν_2(C═O) 1698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.48 (dd, 1H, J = 5.2, 1.2 Hz), 7.16 (dd, 1H, J = 3.6, 1.2 Hz), 7.11 (dd, 1H, J = 4.8, 3.8 Hz), 6.65 (t, 1H, J = 5.8 Hz) 5.12 (d, 2H, J = 5.8 Hz), 2.40 (q, 2H, J = 7.6 Hz), 1.17 (t, 3H, J = 7.6 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 192.4, 174.6, 147.5, 137.0, 129.7, 129.0, 128.8, 127.5, 67.5, 28.0, 9.6; EI MS (*m*/*e*) 224 [M$^+$]; HRMS calcd for $C_{11}H_{12}O_3S$ [M$^+$] 224.05072, found 224.05045.

(*E*)-2-Methylpropionoxy-3-(2-thienyl)-2-propen-1-al (6g): colorless liquid; IR ν_1(C═O) 1736 cm^{-1}, ν_2(C═O) 1678 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.61 (dd, 1H, J = 5.0, 0.8 Hz), 7.62 (s, 1H), 7.45 (dd, 1H, J = 3.8, 0.6 Hz), 7.14−7.19 (m, 1H), 5.05 (s, 2H), 2.32 (q, 2H, J = 7.6 Hz), 1.11 (t, 3H, J = 7.6 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 193.1, 175.0, 146.3, 137.4, 135.5, 134.0, 132.5, 128.9, 56.7, 28.0, 9.7; EI MS (*m*/*e*) 224 [M$^+$]; HRMS calcd for $C_{11}H_{12}O_3S$ [M$^+$] 224.05072, found 224.05118.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for support of this research.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of **2c**, **2d**, **3e**, **4a**−**n**, **5a**−**n**, **6b**−**n**, and **8** and characterization for all starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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