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$Mn(OAc)_3$-promoted sulfur-directed addition of an active methylene compound to alkenes

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ABSTRACT

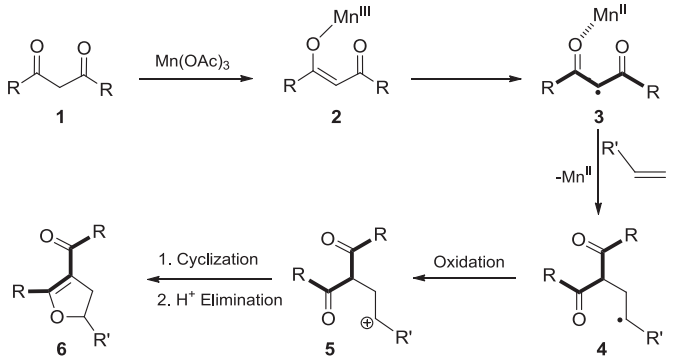
Various alkenes substituted at the 1,2-positions by phenyl, thiophene and furan rings were reacted with 3-(4-methoxyphenyl)-3-oxopropanenitrile in the presence of $Mn(OAc)_3 \cdot 2H_2O$. The exact structure and configuration of the dihydrofuran derivatives formed were determined. In all cases only one regioisomer was formed. The observed regioselectivity was explained on the basis of the formation of a complex between $Mn(OAc)_3$, alkene, and 3-(4-methoxyphenyl)-3-oxopropanenitrile, which directs the mode of the addition to the double bond.

1. Introduction

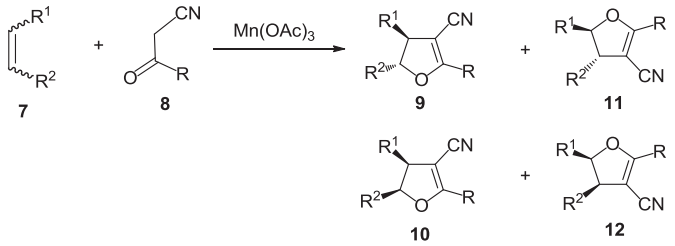
Radical cyclization of alkenes has emerged as a powerful reaction for ring construction.[1] It has been known for a long time that manganese(III) acetate in acetic acid at reflux converts olefins into γ-lactones.[2] Moreover, the reaction of alkenes with 1,3-dicarbonyl compounds **1** in the presence of $Mn(OAc)_3$ in acetic acid forms dihydrofurans **6** (Scheme 1).

Generally, an oxidatively or reductively generated radical **3** can add to a double bond, forming a new radical **4**, which can be reductively or oxidatively terminated. Recently, we have proposed that the cyclization reaction takes place after the oxidation of the radical **4** to the cation **5** to give dihydrofuran derivative **6**.[3]

Fristad and Peterson studied the annulation of a γ-lactone ring onto various unsymmetrically substituted alkenes.[4] They showed that a terminal alkene reacted with a regioselectivity of 40:1, which showed the preference of a secondary radical over a primary radical intermediate. Furthermore, Nishino et al.[5] demonstrated that acylacetonitriles were easily oxidized with manganese(III) acetate in acetic acid to form the corresponding acylcyanomethyl radicals, which attack alkenes to form new 4,5-dihydrofuran-3-carbonitriles at reflux temperature (Scheme 2). More recently, Yilmaz et al.[6] used the same methodology and reported the addition of acylcyanonitriles to various unsymmetrically substituted alkenes.



Scheme 1. General mechanism for addition of 1,3-dicarbonyl compounds to C=C double bonds in the presence of $Mn(OAc)_3$.



Scheme 2. Possible adducts formed by addition of acylacetonitriles to various alkenes in the presence of $Mn(OAc)_3$.

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Addition of acylcyanomethyl radical to unsymmetrically substituted alkenes may provide two regioisomers pairs, **9**/**10** and **11**/**12**. Moreover, the formed regioisomers may be cis or trans (Fig. 2). However, a clear-cut differentiation between the possible regioisomers as well as stereoisomers was not made.[5,6] Assignment of substituent stereochemistry on a dihydrofuran moiety by NMR coupling constant data is difficult. Generally, $J_{trans}>J_{cis}$ is for vicinal hydrogen atoms; however, this is not always the case. In small rings, especially in cyclopropane and cyclobutane, $J_{cis}>J_{trans}$.[7] In the case of a five-membered ring, a conclusion can be made if the conformation of the molecule is known. Antonioletti et al.[8] made the configurational assignments in similar systems using NOE measurements between the relevant protons. A differentiation between the regioisomers was made by the chemical shifts of the ring protons.[6c] This was explained by shielding of this hydrogen by the adjacent C–C bond. This appears to be a useful diagnostic feature. However, a chemical shift difference of about 0.5 ppm may lead to misinterpretation of the spectra. In this paper, we reinvestigated the reaction of 3-(4-methoxyphenyl)-3-oxopropanenitrile with 2-[(*E*)-2-phenylvinyl]thiophene in the presence of $Mn(OAc)_3$.[6c] We were interested in the correct structure of the product and furthermore we wanted to address the question of why one regioisomer was formed exclusively. Moreover, it is interesting to test whether the geometry of alkene used in the reaction has an influence on the geometry of the substituents in the products.

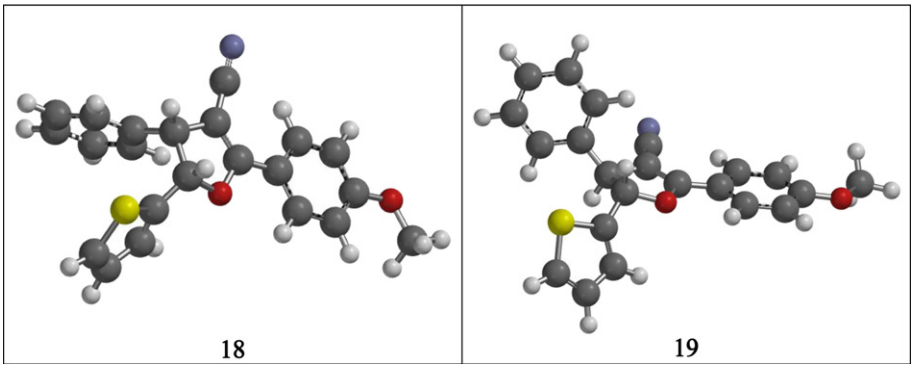
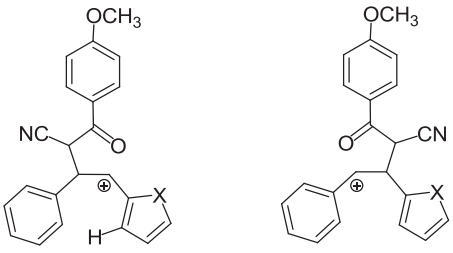


Fig. 1. Optimized geometries of **18** and **19** (DFT, B3LYP at 6-31G** level).



20a X = S
20b X = O

21a X = S
21b X = O

Fig. 2. The structures of possible intermediates **20a**/**20b** and **21a**/**21b**.

2. Results and discussion

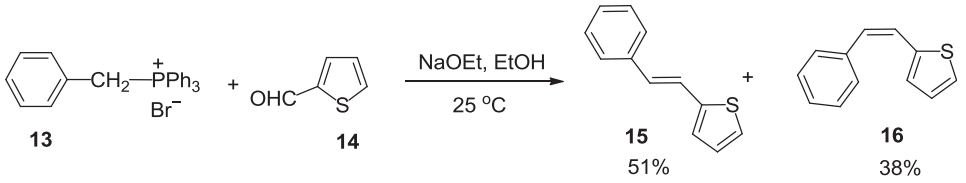
The previously known alkenes **15** and **16** were synthesized as described in the literature.[9] The reaction of benzyltriphenylphosphonium bromide (**13**) with thiophene-2-carbaldehyde (**14**) gave a mixture of *trans*- and *cis*-2-styrylthiophene **15** and **16** in 51% and 38% yields, respectively (Scheme 3). The isomeric mixture was separated on a silica gel column eluting with *n*-hexane. The structural assignments were made on the basis of the measured coupling constants between the double bond protons.

Treatment of pure isomers, *trans*-styrylthiophene (**15**) or *cis*-styrylthiophene (**16**) with 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) in the presence of $Mn(OAc)_3\cdot 2H_2O$ in acetic acid gave the dihydrofuran adduct **18** as the sole isolable product in 47% and 45% yields, respectively (Scheme 4). Careful examination of the reaction mixture did not reveal the formation of any other isolable product. Because of the asymmetric environment of the double bonds in **15** and **16**, the initially formed complex between $Mn(OAc)_3$ and 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) can add to the double bond in two different ways forming the compounds **18** and **19**. However, the expected regioisomer **19** was not detected.

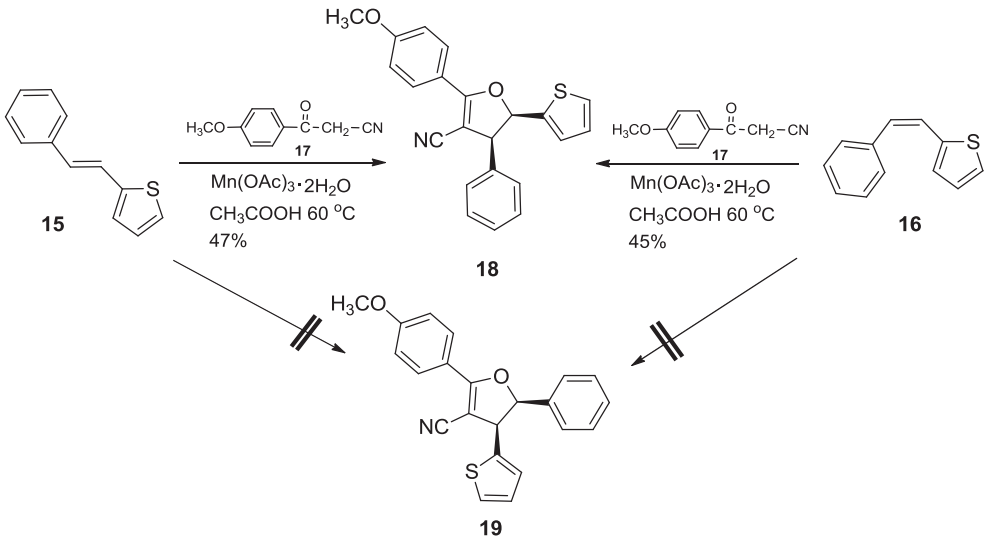
The structure and the configuration of **18** were assigned from ^1H (COSY, DEPT, HSQC, and HMBC) and ^{13}C NMR spectroscopic data. In particular, the HMBC spectrum was very helpful in the assignment of the correct skeleton in **18**. The most conspicuous features in the ^1H NMR spectrum of this compound were the dihydrofuran ring protons. The dihydrofuran ring protons H-4 and H-5 resonate at 4.47 and 5.67 ppm as doublets with a coupling constant of J=7.2 ppm. The low field resonance was assigned to alkoxy proton H-5 due to the inductive effect of the neighboring oxygen atom. In the HMBC spectrum, the H-5 proton resonance at 5.67 ppm correlates with the carbon resonance appearing at 125.9 ppm, which belongs to the β-carbon atom (determined from the HSQC spectrum) of the thiophene ring. Moreover, the C-5 carbon resonance at 87.9 ppm (determined from the HSQC spectrum) correlates with the β-proton H-3′ of the thiophene ring, clearly indicating that alkoxy proton H-5 is closer to the thiophene ring. Furthermore, a three bond correlation between the –CN carbon atom (117.3 ppm) and the H-4 proton resonance appearing at 4.47 establishes the close proximity of the proton H-4 to the nitrile group.

After establishing the correct constitution of **18**, we turned our attention to the configuration of the thiophenyl and phenyl groups. Geometry optimization calculations (DFT, B3LYP at 6-31G** level) on the molecules **18** and **19** show a dihedral angle Φ of 27.2° for $H_4–C_4–C_5–H_5$ in **18** and 147.9° for $H_4–C_4–C_5–H_5$ in **19** (Fig. 1). We calculated the corresponding coupling constants using the Karplus–Conroy equation[10] and obtained ^3J=7.2 Hz for isomer **18** and ^3J=6.6 Hz for the trans-isomer **19**. The theoretically determined value of ^3J=7.2 is in complete agreement with the measured coupling constant of ^3J=7.2. Since the difference between the calculated coupling constants J=7.2 and 6.6 Hz was not large enough to allow an exact assignment, we recorded NOE-DIFF and NOESY spectra. In the NOESY spectrum we observed a strong correlation between the proton resonances appearing at 5.67 (H_5) and 4.47 (H_4). Furthermore, the NOE-DIFF spectrum showed 4.5% and 6.7% signal enhancement of the signals resonating at 5.67 and 4.47 ppm upon irradiation at the resonance frequencies of 4.47 and 5.67 ppm, respectively. All these results together confirmed the cis-configuration of the protons in **18**.

After complete structural characterization of the adduct **18** we turned our attention to the reaction with *cis*-styrylthiophene (**16**). The *cis*-olefin **16** was reacted with 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) and $Mn(OAc)_3\cdot 2H_2O$ in acetic acid under



Scheme 3. Synthesis of *trans*-2-styrylthiophene (**15**) and *cis*-2-styrylthiophene (**16**).

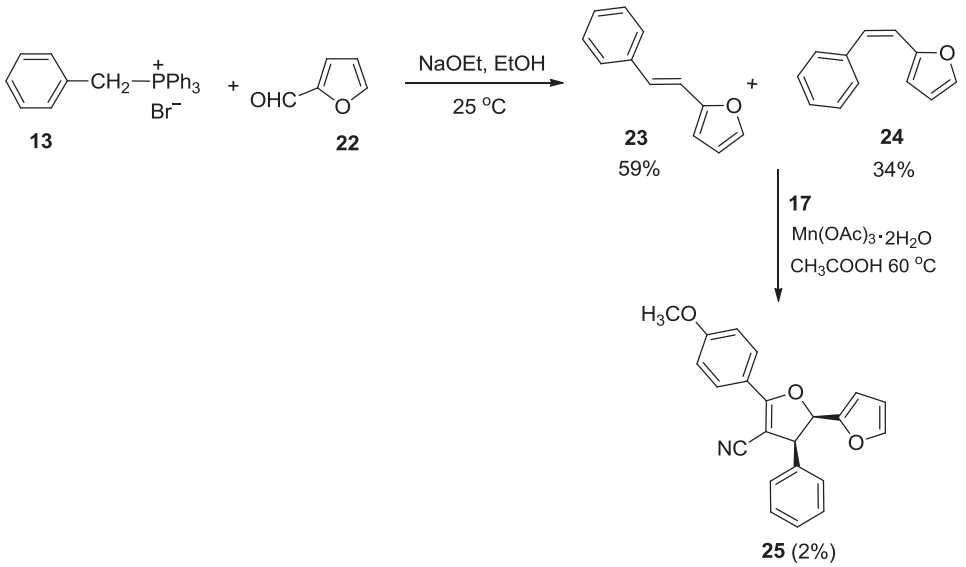


Scheme 4. Reactions of alkenes **15** and **16** with 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) in the presence of $Mn(OAc)_3 \cdot 2H_2O$.

the same reaction conditions. The adduct **18** was formed as the sole isolable product in 45% yield. The spectroscopic data of the product were in agreement with those obtained from the reaction with *trans*-olefin **15**. The configuration of the olefins used in this reaction did not have any effect on the constitution or on the configuration of the final product (Fig. 2).

At this stage we postulate a radical mechanism for the formation of **18**. We assume that a radical having the structure such as **3** resulting from the electron transfer reaction between Mn(III) and **17** serves as a key intermediate and adds regiospecifically to the double bond in **15** and **16**. Oxidation of the radical can form the carbocation **20a**, which undergoes a cyclization reaction to give **18**. It is remarkable to observe that no trace of **19**, which might be derived from the cation **21a**, was formed. We assume that the origin of the observed regioselectivity of the addition of the initially formed radical is controlled by the heteroatom in the five-membered ring. To test the feasibility of this idea we decided to synthesize the corresponding furan derivative **24** and study the behavior of this compound.

trans-Styrylfuran (**23**) and *cis*-styrylfuran (**24**) were synthesized as described in the literature.[11] A mixture of two isomers, **23** and **24** was formed in 59% and 34% yields (Scheme 5). Treatment of those isomers under the same reaction conditions with **17** in the presence of $Mn(OAc)_3 \cdot 2H_2O$ resulted in the formation of only



Scheme 5. Synthesis of *trans*-2-styrylfuran (**23**) and *cis*-2-styrylfuran (**24**) and their reaction with 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) in the presence of $Mn(OAc)_3 \cdot 2H_2O$.

one isolable product, **25**, in only 2% yield. The structure of this product was determined using 1D- and 2D-NMR spectral measurements. In particular, the HMBC spectrum of **25** supports the correct structure. The proton signal H-4 appearing at 4.73 ppm correlates with the α-carbon resonance of the benzene ring; furthermore, a correlation between the nitrile carbon and H-4 proton supports the presumption that **25** has a similar structure to **18**. For the formation of this compound we propose **20b** as the intermediate. However, the furan ring cannot stabilize a positive charge as much as the benzene ring. Again, we assume that the heteroatom (oxygen atom in furan ring in **23** and **24**) has a directing effect to determine the regiospecific addition of the initially formed radical species having a structure like **3** to the double bond in **23** and **24**.

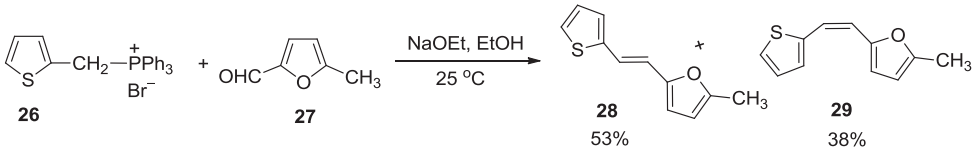
Comparison of these results obtained from **15**/**16** and **23**/**24** shows that the yields for the formation of dihydrofuran ring in the case of **23** and **24** are very low (2%). We assume that the furan ring undergoes some kind of reaction at the α-position or polymerization. To prevent any reaction at the α-position of the furan ring, this position was blocked with a methyl group.

The desired olefins **28** and **29** were synthesized by Wittig reaction of 5-methylfuran-2-carbaldehyde **27** with triphenylphosphonium salt **26**,[12] prepared from 2-(bromomethyl)thiophene with triphenylphosphine (Scheme 6). The isomers **28** and **29** formed in 53% and 38% yields were separated by column chromatography on silica gel. The structural assignments were made using ^{1}H and ^{13}C NMR spectroscopy.

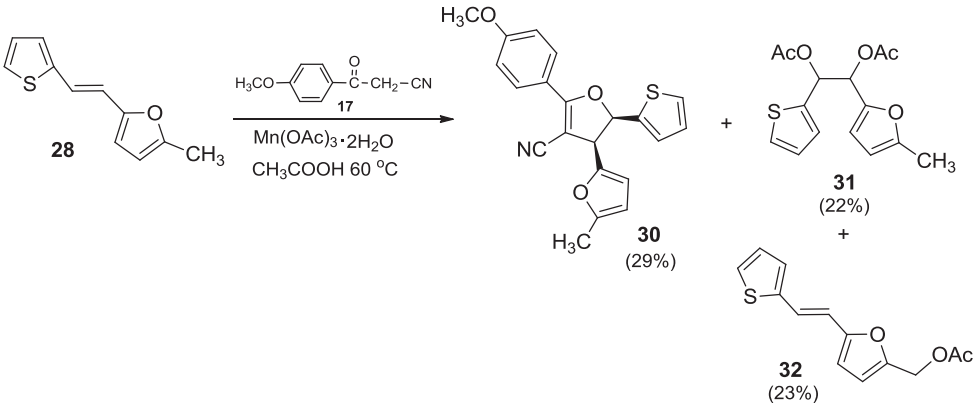
The reaction of trans-isomer **28** as well as a mixture of **28** and **29** with 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) was accomplished with $Mn(OAc)_3 \cdot 2H_2O$ in acetic acid, and three products were isolated. In contrast to the reactions with **15**/**16** and **28**/**29**, significantly different products **31** and **32** were formed beside the expected adduct **30**, in 22%, 23% and 29% yields, respectively (Scheme 7). Blocking of the α-position in furan increased the yield of the products. The major product was the expected addition product **30**. Careful examination of the reaction mixture did not reveal the formation of any other regioisomer. The structure and configuration of **30** were assigned from ^{1}H (COSY, HSQC, HMBC) and ^{13}C NMR spectroscopic data. A correlation between the nitrile carbon atom and H-4 proton in the HMBC spectrum clearly indicated the correct structure and the mode of the addition as we discussed in other cases. The second product, **31**, which was formed as a single diastereomeric isomer, derives from successive oxidation of the double bond in **28** followed by capture by acetate anions. The last isomer, **32**, is formed by proton abstraction of one of the methyl protons followed by oxidation and substitution by acetate anion.

In all three different systems **15**/**16**, **23**/**24**, and **28**/**29**, the formation of only one regioisomer can be rationalized by regioselective addition of the initially formed radical derived from 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) to the double bond in those systems followed by oxidation with $Mn(OAc)_3$ to a classical cation, which can undergo rapid cyclization with the enol form of **17**. In the case of **15**/**16** we assume that the heteroatom sulfur in the thiophene ring has a directing effect for the mode of the addition, although in the case of the formation of the other regioisomer **19** (not observed) the formed cation **21a** and **21b** would be more stabilized due to conjugation with the benzene ring.[13] When the thiophene ring in **15**/**16** is replaced by a furan ring, high regioselectivity was also observed. This result shows that the oxygen atom also has a similar directing effect. However, in the case of a mixed system (**28**/**29**), the formation of a single regioisomer is remarkable. One would expect competition between two different heteroatoms. The fact that this is not the case clearly indicates the dominating effect of the sulfur atom. On the basis of these results the following mechanism is suggested for the addition process (Scheme 8).

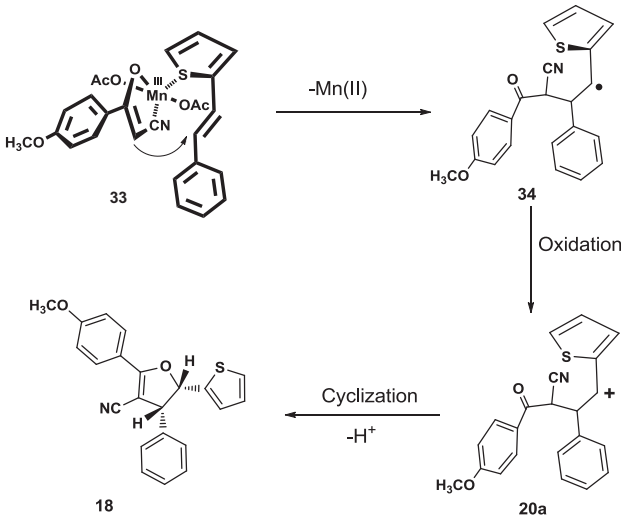
We propose that the complex **33** is formed between $Mn(OAc)_3$, alkene, and 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) at the first stage. The next step is the electron transfer from the alkene to the metal center and the formation of a C–C bond between the active methylene group in **17** and the double bond carbon atom directly connected to the benzene ring because of close proximity. However, the formation of a C–C bond between the



Scheme 6. Synthesis of *trans*- and *cis*-2-methyl-5-(2-(thiophen-2-yl)vinyl)furan (**28**) and (**29**).



Scheme 7. Reaction of *trans*-2-methyl-5-(2-(thiophen-2-yl)vinyl)furan (**28**) with 3-(4-methoxyphenyl)-3-oxopropanenitrile (**17**) in the presence of $Mn(OAc)_3 \cdot 2H_2O$.



Scheme 8. Mechanism of formation of **18**.

carbon atom connected to the thiophene ring and the active methylene carbon in **17** is probably hindered due to geometrical restriction.

In conclusion, the sulfur atom in **15**/**16** and **28**/**29** and the oxygen atom in **23**/**24** are directing the mode of the addition reactions. In order to obtain further evidence about the directing effect of heteroatoms we are currently examining different systems in which the distance between the heteroatom and alkene is varied.

3. Experimental section

3.1. General

Infrared spectra were obtained from a solution ($CHCl_3$) in 0.1 mm cells or KBr pellets on an FT-IR Bruker Vertex 70 instrument. The ^1H and ^{13}C NMR spectra were recorded on a Bruker-Biospin (DPX-400) instrument. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60 mesh, Merck), TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates.

3.2. (*Z*)-2-Styrylthiophene (16) and (*E*)-2-styrylthiophene (15)

Benzyltriphenylphosphonium bromide (**13**) (4.5 g, 10.4 mmol) was added to a sodium ethoxide solution in ethanol, prepared by addition of metallic sodium (0.29 g, 12.5 mmol) to 50 mL of EtOH. After dissolving of all phosphine reagent, thiophene-2-carbaldehyde (**14**) (1.06 g, 9.46 mmol) was added to reaction mixture. The resulting mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness first. Then water was added and the mixture was extracted with methylene chloride (2×50 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. Removal of solvent gave 2.90 g crude product, which was chromatographed over silica gel (150 g) eluting with hexane to give the isomers **15** and **16**.

(*Z*)-2-*Styrylthiophene* (**16**) was isolated as the first fraction: colorless liquid, 670 mg, 38% (isolated yield). (*E*)-2-*Styrylthiophene* (**15**) was isolated as the second fraction: colorless crystals, mp 110–111 °C (from *n*-hexane/ethyl acetate, lit. 111–112 °C[9b]), 0.9 g, 51.1% (isolated yield). The spectral data of these compounds were consistent with those reported in the literature.[9]

3.3. Reaction of (*E*)-2-styrylthiophene (15) with 3-(4-methoxyphenyl)-3-oxopropanenitrile in the presence of $Mn(OAc)_3$

$Mn(OAc)_3 \cdot 2H_2O$ (402 mg, 1.5 mmol) was dissolved in 20 mL of glacial acetic acid and the flask was heated to 60 °C under nitrogen. Then a mixture of 2-strylthiophene (**15**) (100 mg, 0.54 mmol) and 3-(4-methoxyphenyl)-3-oxopropanenitrile (**13**) (185 mg, 1.06 mmol) in 5 mL of glacial acetic acid was added dropwise to the $Mn(OAc)_3$ solution. The reaction mixture was stirred for 12 h at 60 °C under nitrogen. Water (50 mL) was added and the mixture was stirred additional 10 min. The reaction mixture was cooled to room temperature and the solution was extracted with methylene chloride (3×50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution and then with water and dried ($MgSO_4$). Evaporation of the solvent gave the crude compound. The chromatography of the residue on silica gel (3:1 hexane/EtOAc) gave 89 mg (47%, isolated yield) of **18** as colorless solid, mp 84–86 °C, (lit. 85–86 °C[6c]), *rel*-(4*R*,5*S*)-2-(4-*methoxyphenyl*)-4-*phenyl*-5-(2-*thienyl*)-4,5-*dihydrofuran*-3-*carbonitrile* (**18**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.90 (quasi d, AA′-part of AA′XX′-system, 2H, benzene), 7.32–7.21 (m, 6H, five benzene, one thiophene), 6.99 (br d, *J*=4.6 Hz, 1H, thiophene), 6.93 (dd, *J*=5.1 and 4.6 Hz, 1H, thiophene), 6.91–6.86 (quasi d, XX′-part of AA′XX′-system, 2H, benzene), 5.67 (d, *J*=7.2 Hz, 1H), 4.47 (d, *J*=7.2 Hz, 1H), 3.76 (s, 3H, OCH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.2 (C-5), 162.3 (C-4), 141.9 (C-2′) 139.3 (C-1), 129.3 (C-2 and C-6) 129.2 (C-3 and C-5), 128.2 (C-4), 127.5 (C-2 and C-6), 127.0 (C-4′), 126.3 (C-5′), 125.9 (C-3′), 120.1 (C-1), 117.3 (C≡N), 114.1 (C-3 and C-5), 87.9 (C-2), 82.3 (C-4), 55.4 (OCH_3), 58.8 (C-3).[6c]

3.4. Reaction of (*Z*)-2-styrylthiophene (15) with 3-(4-methoxyphenyl)-3-oxopropanenitrile in the presence of $Mn(OAc)_3$

$Mn(OAc)_3 \cdot 2H_2O$ (1.24 g, 4.65 mmol), 2-strylthiophene (**15**) (293 mg, 1.55 mmol), and 3-(4-methoxyphenyl)-3-oxopropanenitrile (**13**) (550 mg, 3.14 mmol) was reacted as described above to give 250 mg (45%, isolated yield) of **18** as orange solid, mp 84–86 °C.

3.5. (*Z*)-2-Styrylfuran (24) and (*E*)-2-styrylfuran (23)

Benzyltriphenylphosphonium bromide (**13**) (7.67 g, 17.7 mmol), sodium ethoxide solution in ethanol, prepared by addition of metallic sodium (0.42 g, 18.3 mmol) to 50 mL of EtOH and furfural (1.54 g, 16 mmol) was reacted as described above for the synthesis of **15** and **16**. The crude product, which was chromatographed over silica gel (150 g) eluting with hexane gave the isomers **24** and **23**. 2-[(*Z*)-2-*phenylethenyl*]*furan* (**24**) was isolated as the first fraction: colorless liquid, 930 mg, 34% (isolated yield). 2-[(*E*)-2-*phenylethenyl*]*furan* (**23**) was isolated as the second fraction: colorless crystals, mp 51–52 °C (from *n*-hexane/ethyl acetate, lit. 53–54 °C[11e]), 1.62 g, 59% (isolated yield). The spectral data of these compounds were consistent with those reported in the literature.[11]

3.6. Reaction of (*Z*)-2-styrylfuran (15) with 3-(4-methoxyphenyl)-3-oxopropanenitrile in the presence of $Mn(OAc)_3$

$Mn(OAc)_3 \cdot 2H_2O$ (2.27 mg, 8.46 mmol), 2-strylthiophene (**24**) (480 mg, 2.82 mmol), and 3-(4-methoxyphenyl)-3-oxopropanenitrile (**13**) (988 mg, 5.64 mmol) was reacted as described above to give 19.4 mg (2%) of **25** as yellow oil. *rel*-(4*R*,5*S*)-5-(4-*Methoxyphenyl*)-3-*phenyl*-2,3-*dihydro*-2,2′-*bifuran*-4-*carbonitrile* (**25**). ^1H

NMR (400 MHz, $CDCl_3$) δ 8.00 (quasi d, J=9.0 Hz, 2H, H-2 and H-6), 7.49 (d, $J_{5',4'}$=1.8 Hz, 1H, H-5′), 7.38–7.27 (m, 5H, benzene), 6.94 (quasi d, J=9.0 Hz, 2H, H-3 and H-5), 6.45 (d, $J_{3',4'}$=3.3 Hz, 1H, H-3′), 6.39 (dd, $J_{4',3'}$=3.3 and $J_{4',5'}$=1.8 Hz, 1H, H-4′), 5.52 (d, $J_{2,3}$=7.9 Hz, 1H, H-2), 4.73 (d, $J_{3,2}$=7.9 Hz, 1H, H-3), 3.85 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C-5), 162.3 (C-4), 150.6 (C-2′), 143.9 (C-5′), 139.4 (C-1), 129.3 (C-2 and C-6), 129.2 (C-3 and C-5) 128.1 (C-4), 127.6 (C-2 and C-6), 120.2 (C-1), 117.5 (C≡N), 114.1 (C-3 and C-5), 110.6 (C-4′), 109.8 (C-3′), 84.9 (C-2), 82.3 (C-4), 55.4 (OCH_3), 54.5 (C-3). MS (m/z, relative intensity): 343.2/344.2 (M^+, 4/1), 314.1 (M-CHO), 135.1.

3.7. Reaction of (*E*)-2-styrylfuran (23) with 3-(4-methoxyphenyl)-3-oxopropanenitrile in the presence of $Mn(OAc)_3$

$Mn(OAc)_3\cdot 2H_2O$ (470 mg, 1.77 mmol), 2-strylthiophene (**24**) (480 mg, 2.82 mmol), and 3-(4-methoxyphenyl)-3-oxopropanenitrile (**13**) (206 mg, 1.18 mmol) was reacted as described above to give 5.0 mg (2%) of **25** as yellow oil.

3.8. (*E*)-2-Methyl-5-(2-(thiophen-2-yl)vinyl)furan (28) and (*Z*)-2-methyl-5-(2-(thiophen-2-yl)vinyl)furan (29)

Metallic sodium (0.33 g, 14.2 mmol) was divided into small pieces and dissolved in 50 mL of ethanol gently at room temperature. After complete dissolving, benzyltriphenylphosphonium bromide (**1**) (6.21 g, 14.1 mmol) was added to sodium ethoxide solution. Then 5-methylfurfural (**27**) (1.42 g, 12.9 mmol) was added to reaction mixture. The resulting mixture was stirred overnight at room temperature and evaporated to dryness. Then water was added and the mixture was extracted with 50 mL of methylene chloride (2×50 mL). The combined organic extracts were dried over $MgSO_4$. Removal of the solvent gave 2.23 g crude product, which was chromatographed on silica gel (150 g) eluting with hexane give 900 mg (37%) of **29** as colorless liquid and 1.24 g of (51%) (*E*)-2-methyl-5-(2-(thiophen-2-yl)vinyl)furan **(5)** as colorless liquid. (*E*)-2-*methyl*-5-(2-(*thiophen*-2-*yl*)*vinyl*)*furan* (**29**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (br d, J=5.0 Hz, 1H, thiophene), 7.00 (d, J=16.0 Hz, 1H, C═CH), 6.94 (d, A-part of AB-system, J=3.6 Hz, 1H, thiophene), 6.90 (dd, B-part of AB-system, J=5.0 and 3.6 Hz, 1H, thiophene), 6.57 (d, J=16.0 Hz, 1H, HC═C), 6.13 (d, J=3.1 Hz, 1H, furan), 5.95–5.90 (m, 1H, furan), 2.26 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.2, 143.0, 127.7, 125.6, 123.8, 118.7, 116.4, 110.0, 107.9, 13.8; IR (ATR, cm^{-1}) 3105, 2947, 2917, 1588, 1543, 1423, 1019, 940, 778, 693. HRMS: m/z (M) calcd for $C_{11}H_{10}OS$: 190.0452. Found: 190.0444. (*Z*)-2-*Methyl*-5-(2-(*thiophen*-2-*yl*)*vinyl*)*furan* (**29**). Purity 90%, a mixture with (*E*)-isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (br d, J=3.6 Hz, 1H, thiophene), 7.18 (br d, J=5.1 Hz, 1H, thiophene), 6.93 (dd, J=5.1 and 3.6 Hz, 1H, thiophene), 6.35 (d, A-part of AB-system, J=12.9 Hz, 1H, C═CH), 6.30 (d, J=3.2 Hz, 1H, furan), 6.06 (d, B-part of AB-system, J=12.9 Hz, 1H, HC═C), 5.91 (br d, J=3.2 Hz, 1H, furan) 2.29 (s, 3H, CH_3).

3.9. Reaction of (*E*)-2-methyl-5-(2-(thiophen-2-yl)vinyl)furan (29) with 3-(4-methoxyphenyl)-3-oxopropanenitrile in the presence of $Mn(OAc)_3$

$Mn(OAc)_3\cdot 2H_2O$ (2.41 g, 8.99 mmol) was dissolved in 50 mL of glacial acetic acid under nitrogen. Then a solution of (*E*)-olefin (**29**) (570 mg, 3 mmol) and 3-(4-methoxyphenyl)-3-oxopropanenitrile (1.05 g, 6 mmol) in 10 mL of acetic acid was added to $Mn(OAc)_3$ solution. The reaction mixture was stirred 12 h at 60 °C and under inert atmosphere. Water (50 mL) was added and stirred for additional 10 min. The reaction mixture was cooled to room temperature and extracted with methylene chloride (3×50 mL). Combined organic phases were washed with saturated $NaHCO_3$ dried over $MgSO_4$. After evaporation of solvent the residue was chromatographed on silica gel (150 g) eluting with hexane/EtOAc (4:1) then successive flash chromatography eluting with hexane/EtOAc (7:1) to give three compounds in the following order **30** (320 mg, 29.1%), **31** (200 mg, 22%), and **32** (170 mg, 23%). *rel*-(4*R*,5*S*)-2-(4-*Methoxyphenyl*)-4-(5-*methylfuran*-2-*yl*)-5-(*thiophen*-2-*yl*)-4,5-*dihydrofuran*-3-*carbonitrile* (**30**) was isolated as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (quasi d, AA′-part of AA′XX′-system, J=9.0 Hz, 2H, benzene), 7.20 (dd, J=5.0 and 1.2 Hz, 1H, thiophene), 6.96–6.95 (m, 1H, thiophene), 6.92 (dd, J=5.1 and 3.5 Hz, 1H, thiophene), 6.88 (quasi d, XX′-part of AA′XX′-system, J=9.0 Hz, 2H, benzene), 6.32 (d, J=3.2 Hz, 1H, furan), 5.95–5.90 (m, 1H, furan), 5.44 (d, J=8.4 Hz, 1H, H-5), 4.98 (d, J=8.4 Hz, 1H, H-4), 3.79 (s, 3H, $-OCH_3$), 2.26 (s, 3H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.3, 154.2, 147.9, 142.6, 129.4, 127.4, 125.7, 125.5, 120.2, 114.11, 114.07, 111.5, 106.7, 85.1, 82.4, 55.5, 49.4, 13.8. IR (ATR, cm^{-1}) 2933, 2205, 1738, 1608, 1512, 1261, 1179, 908, 732. HRMS: m/z $(M+H)^+$ calcd for $C_{21}H_{17}NO_3S$: 364.1002; found: 364.1047. 1-(5-*Methylfuran*-2-*yl*)-2-(*thiophen*-2-*yl*)*ethane*-1,2-*diyl diacetate* (**31**) was isolated as the second fraction colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J=5.0, 1.1 Hz, 1H, thiophene), 6.86 (br d, J=3.6 Hz, 1H, thiophene), 6.80 (dd, J=5.0 and 3.6 Hz, 1H, thiophene), 6.53 (d, J=8.5 Hz, 1H, HC—C), 6.06 (d, J=2.7 Hz, 1H, furan), 6.05 (d, J=8.5 Hz, 1H, C—CH), 5.78–5.73 (m, 1H, furan), 2.18 (s, 3H, $-CH_3$), 2.02 (s, 6H, 2× $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.6, 152.9, 146.7, 138.4, 126.9, 126.6, 126.1, 111.7, 106.4, 70.3, 70.1, 20.99, 20.95, 13.6. IR (ATR, cm^{-1}) 2957, 1743, 1370, 1214, 1020, 729, 707. HRMS: m/z $(M+Na)^+$ calcd for $C_{15}H_{16}O_5S$: 331.0611; found: 331.0686. (*E*)-(5-(2-(*Thiophen*-2-*yl*)*vinyl*)*furan*-2-*yl*)*methyl acetate* (**32**) was isolated as the third fraction. Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J=5.1 Hz, 1H, thiophene), 7.11 (d, J=16.0 Hz, 1H, C═CH), 6.99 (br d, J=3.6 Hz, 1H, thiophene), 6.92 (dd, J=5.1 and 3.6 Hz, 1H, thiophene), 6.60 (d, J=16.0 Hz, 1H, HC═C), 6.35 (d, A-part of AB-system, J=3.3 Hz, 1H, furan), 6.21 (d, B-part of AB-system, J=3.3 Hz, 1H, furan), 4.99 (s, 2H, CH_2), 2.04 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 153.5, 149.0, 142.3, 127.7, 126.4, 124.6, 121.2, 115.7, 112.8, 109.3, 58.2, 30.9; IR (ATR, cm^{-1}) 2923, 1739, 1232, 1019, 907, 729, 699. HRMS: m/z (M^+) calcd for $C_{13}H_{12}O_3S$: 248.0507; found: 248.0509.

3.10. Reaction of a mixture of 28 and 29 with 3-(4-methoxyphenyl)-3-oxopropanenitrile in the presence of $Mn(OAc)_3$

When a mixture of **28** and **29** was used instead of pure isomers, the same compounds were isolated almost with same products ratio.

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Supplementary data

These data include the ^{1}H- and ^{13}C NMR spectra of eleven compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.05.003.

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