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Research Note

Synthesis and Singlet Oxygen Reactivity of 1,2-Diaryloxyethenes and Selected Sulfur and Nitrogen Analogs

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ABSTRACT

1,2-Diaryloxyethene has recently been proposed as a linker in singlet oxygen-mediated drug release. Even though 1,2-diaryloxyethenes look very simple, their synthesis was not an easy task. Previous methods are limited to symmetric molecules, lengthy step and low yield. We report on a facile synthetic method not only for 1,2-diaryloxyethenes but also their sulfur and nitrogen analogs in yields ranging from 40 to 90% with more than 90% purity at the vinylation reaction.

INTRODUCTION

Electron-rich olefins can be used as reagents in organic synthesis. Among other things vinyl ethers are reagents for cycloadditions (1,2), cyclopropanations (3) and polymer syntheses (4). Vinyl amines are also used in the preparation of polymer dyes, and catalysis and ion-exchange resins. Singlet oxygen being an electrophilic reagent can react with electron-rich olefins *via* ene reactions and 1,2-cycloadditions, and with conjugated dienes *via* 1,4-cycloadditions. 1,2-Cycloaddition reactions of singlet oxygen to olefinic bonds form dioxetanes that spontaneously fragment to generate two carbonyl products (Scheme 2; 5–10). The 1,2-cycloaddition reaction of singlet oxygen has been proposed for phototriggerable drug delivery systems in the form of liposomes, cyclodextrin complexes and prodrugs (11–13). Screening of various 1,2-substituted olefins resulted in the choice of 1,2-dioxy, 1,2-dithioxy, 1-oxy and 1-thioxy olefins (vinyl groups activated by heteroatoms) for the singlet oxygen-cleavable linkers (14). In particular, 1,2-diaryloxyethene was proposed for site specific prodrug release and its singlet oxygen-mediated cleavage in solutions was demonstrated (15).

While considerable efforts have recently been made to develop synthetic methods for monosubstituted olefins (16), there have been a number of publications for the syntheses of 1,2-diheteroatom-substituted olefins (17–19). With the exception of (2-aryloxyvinyl)phenyl sulfanes, which were synthesized by the reaction of benzenesulfenyl chloride with vinylaryl ethers (20–23), all the synthetic processes are limited only for symmetric molecules and to procedures that lead to low yield or nonstereospecificity (mixture of *Z* and *E* isomers) (17–19). Lengthy multiple steps are also required and some of the processes required harsh reaction conditions. For example, 1,2-diphenoxyethene has been synthesized from ethylene chlorohydrins in a seven step sequence involving high pressure and temperature (24). The other method for the same compound involved chlorination and dehydrochlorination of 1,2-diphenoxyethane (18). This method is limited for the synthesis of symmetric molecules and yields a mixture of *E* and *Z* products in low yields. The most recent method for the preparation of 1,2-diphenoxyethene and derivatives involved bromination followed by stereospecific debromination to give either *E*- or *Z*- product (17). This method is also limited to symmetric 1,2-diaryloxyethenes using harsh conditions and providing low yields.

Recently, light-controlled drug release has attracted much attention for new drug delivery systems (12,15,25,26). However, the limited synthetic methods for 1,2-diheteroatom-substituted olefins have been one of the major hurdles. Thus, versatile, efficient and stereospecific synthetic routes should be developed for these applications. Herein, we describe the first facile synthetic approach for *E*-1,2-diheteroatom-substituted olefins (R-O[H]C = CX[H]-R′: X = O, N, or S, Scheme 1). It is a versatile, efficient and stereospecific method in as few as four steps from starting materials. We have been able to demonstrate that the chemistry can be used for preparation of both symmetrically (R-O[H]C = C[H]O-R) and asymmetrically diheteroatom-substituted (R-O[H]C = C[H]O-R′, R-O[H]C = C[H]S-R′; R-O[H]C = C[H]N-R′) olefins from a variety of common functional groups such as –OH, –NH and SH. The photooxidation of those olefins that were not tested in our previous article is also reported.

MATERIALS AND METHODS

All solvents and reagents were used as obtained from Sigma–Aldrich and Thermo Fisher Scientific unless otherwise stated. All reactions were monitored by TLC using 5–17 μm silica gel plates with fluorescent indicators from Sigma–Aldrich. All column chromatography was carried out using 40–63 μm silica gel from Sorbent Technologies. NMR spectra were recorded at 25°C using a 300 or 400 MHz Spectrometer. NMR solvents with residual solvent signals were used as

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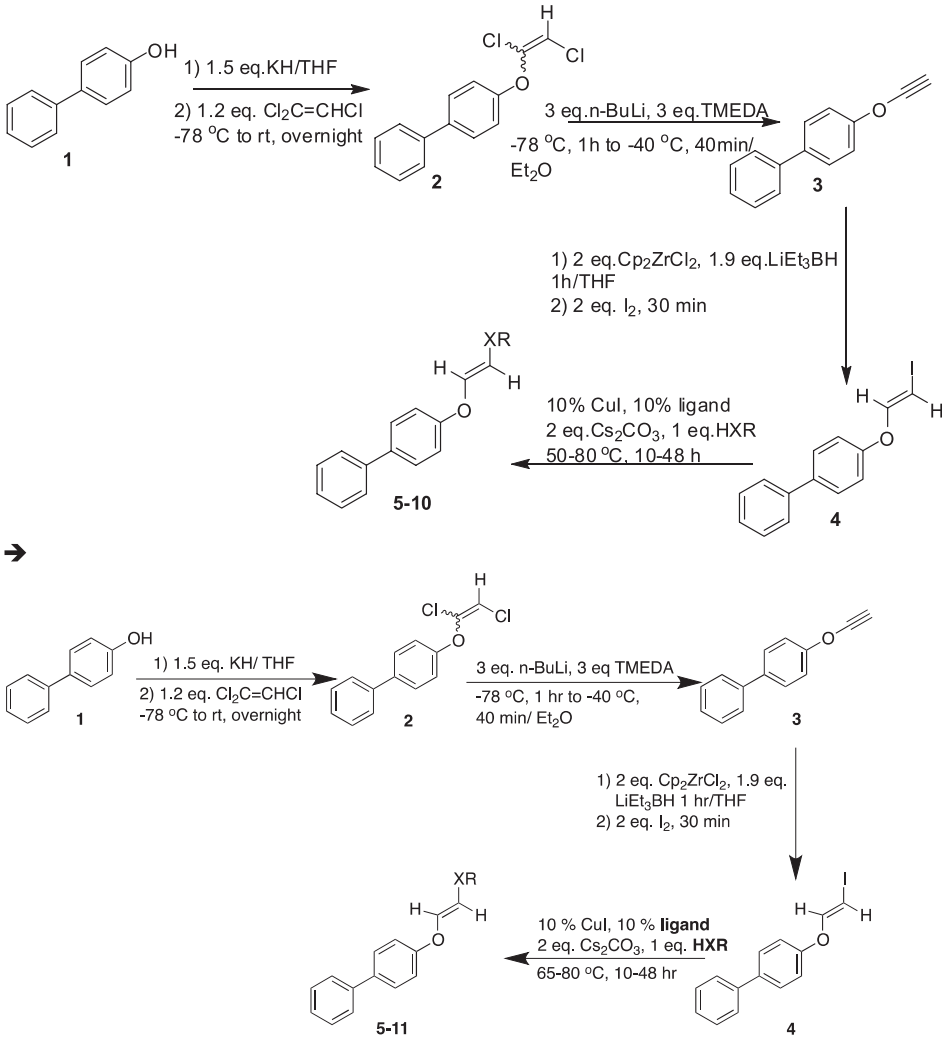


Scheme 1. Synthetic route for vinyl diether and its analogs.

internal standards. ESI mass spectrometry was collected at facilities at South Dakota State University, University of Oklahoma, or University of Buffalo. IR spectra were recorded on a BioRad FT-155FT-IR spectrometer (using dichloromthane as solvent). Melting points were determined using a Mel-temp® Electrothermal instrument. Elemental analyses were performed at Atlantic Microlab, Inc. HPLC analysis was performed with HP Agilent 1100 (Column: Thermo Fisher Scientific, Hypersil, BDS 5 μm, C18 column, 5 μm particle size, 250 mm length × 4.6 mm inner diameter; mobile phase: 90/10 [acetonitrile/water]; flow rate: 1 mL min^{-1}; detection: 254 nm). Photooxidation of olefins were performed using 690 nm diode laser (model #: MRL-690[FC], Changchun New Industries).

4-((1,2-Dichlorovinyl)oxy)-1,1′-biphenyl (2). To a two-necked, round bottom flask (250 mL) equipped with a magnetic stirrer, pressure equalizing funnel and rubber septum was suspended in oil free potassium hydride (2.23 g, 55 mmoL, 1.5 eq) in tetrahydrofuran (THF, 25 mL). 4-Phenylphenol (6.30 g, 37 mmoL, 1 eq) in THF (50 mL) was then added drop-wise with stirring for over 20 min *via* the funnel. After the evolution of hydrogen was complete, the orange-yellow slurry was cooled to −78°C, and then treated with drop-wise solution of trichloroethylene (5.8 g, 44 mmoL, 1.2 eq) in THF (25 mL) for over 10 min. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature (rt) and then maintained for overnight (12 h). To the dark brown mixture was carefully added water (10 mL) using a syringe and then partitioned between water (200 mL) and ethyl acetate (200 mL). The organic phase was then washed with brine (200 mL). Extraction of the combined aqueous layers was carried out using ethyl acetate (150 mL × 3). The combine organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated using the rotary evaporator to give yellowish brown oil. Silica gel (200 g) column chromatography was carried out using hexane as eluent to afford 2 (10.5 g, 85%) as colorless oil that later crystallized to white crystals: mp 52–55°C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.62–7.54 (m, 4H, HAr), 7.48–7.41 (m, 2H, HAr), 7.39–7.32 (m, 1H, HAr), 7.18–7.12 (m, 2H, HAr), 6.00 (s, 1H, HC(Cl) = C(O)) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): 153.3, 140.2, 137.8, 128.8, 128.5, 127.3, 127.0, 117.4, 103.9 ppm; IR (cm^{-1}): 3105, 3031, 1898, 1658, 1630, 1603, 1585, 1543, 1310, 1203, 1184, 1107, 1074, 1008, 996, 915, 863, 840, 641, 547, 511; HRMS (ESI) calculated for $C_{14}H_{10}Cl_2O$ $[M\text{-}H]^-$ 263.0031; found 263.0030; elemental analysis calculated for $C_{14}H_{20}Cl_2O.0.02H_2O$: C, 63.33; H, 3.81; found: C, 63.34; H, 3.79.

4-(Ethynyloxy)-1,1′-biphenyl (3). To a two-necked, round-bottomed flask (100 mL) equipped with a nitrogen inlet adapter and rubber septum was added the vinyl ether **2** (2.0 g, 7.6 mmoL, 1 eq), anhydrous diethyl ether (30 mL) and TMEDA (23 mmoL, 3.3 mL, 3 eq), and then cooled at −78°C. 2.5 M *n*-Butyllithium (9.0 mL, 23 mmoL, 3 eq) was then added drop-wise to the reaction mixture for over 5 min. The reaction mixture was then maintained at −78°C and −40°C for 1 h and 40 min respectively, and then cooled to −78°C, whereas 10% ethanol in pentane (10 mL) was added drop-wise. After 10 min, the reaction mixture was then diluted with *n*-pentane (20 mL) and then washed with saturated solution of ammonium chloride (25 mL). The organic phase was later washed twice with water (20 mL) and then finally with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give brown oil. The oil was purified by column chromatography with

hexane as the eluent to yield **3** as dark brown oil (0.84 g, 70%) that later crystallized out as brown amorphous solid: mp 48–49°C. The compound was placed in a round bottom flask and flushed with nitrogen and kept at −78°C to avoid the decomposition if it was not to be used immediately. ^{1}H NMR (300 MHz, $CDCl_3$): 7.64–7.52 (m, 4H, HAr), 7.48–7.41 (m, 2H, HAr), 7.40–7.34 (m, 3H, HAr), 2.13 (s, 1H,≡–H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): 155.0, 140.1, 138.0, 128.9, 128.4, 127.4, 127.0, 115.4, 84.5, 33.5 ppm; IR (cm^{-1}): 3317 (≡C–H), 3029, 2927, 2174 (C≡C), 1606, 1512, 1484, 1208, 1166, 1062, 1008, 941, 838, 641, 548, 450; HRMS (ESI) calculated for $C_{14}H_{10}O$ $[M\text{-}H]^-$ 193.0654; found 193.0651; elemental analysis calculated for $C_{14}H_{10}O.0.13H_2O$: C, 85.54; H, 5.26; found: C, 85.54; H, 5.38.

(E)-4-((2-Iodovinyl) oxy)-1,1′-biphenyl (4). To an oven dried, two-necked flask (250 mL) under nitrogen and protected from light was added Cp_2ZrCl_2 (5.2 g, 20.3 mmoL, 2 eq), dry THF (30 mL) and 1 M lithium triethylborohydride (super hydride) in THF (20 mL, 20 mmoL, 1.9 eq). The mixture was stirred for 1 h where the alkyne **3** (1.97 g, 10.2 mmoL, 1 eq) was added. After 30 min, iodine (2.57 g, 20.3 mmoL, 2 eq) was added and the reaction mixture was stirred for 30–40 min, protected from light. The reaction was quenched by diluting with ethyl acetate/hexane (1:1, 50 mL). The diluted mixture was then washed twice with saturated solution of sodium bicarbonate (150 mL) and the combined aqueous layers were extracted with ethyl acetate/hexane mixture (1:1). Ten percentage aqueous sodium thiosulphate (100 mL) was used to wash the combined organic phases followed by brine (100 mL), dried over sodium sulfate, filtered, concentrated to yellowish slurry, which was purified by silica gel column chromatography using 100% hexane as eluent (silica gel was pretreated with 2.5% vol/vol triethylamine) to afford **4** as white amorphous crystals (1.80 g, 55%): mp 64–66°C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.64–7.52 (m, 4H, HAr), 7.49–7.41 (m, 2H), 7.38–7.32 (m, 1H, HAr), 7.13–7.01 (m, 3H, HAr), 5.74 (s, 1H, CH = CH, J = 12.2 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): 155.5, 150.3, 140.3, 137.0, 128.9, 128.4, 127.2, 126.9, 117.5, 57.9 ppm; IR (cm^{-1}): 3316, 3077, 3034, 2960, 2924, 2874, 2174, 1643, 1623, 1601, 1515, 1485, 1330, 1307, 1226, 1186, 1173, 1093, 1008, 919, 854, 837, 697, 579, 549.

General procedure for coupling reactions using 2-pyridin-2yl-1H-benzoimidazole (L2): (E)-4-((2-(Phenoxy) vinyl) oxy)-1,1′-biphenyl (5). An oven dried, three-necked, round-bottomed flask (50 mL) equipped with a nitrogen inlet, reflux condenser, rubber septum was repeatedly evacuated and back-filled with dry and pure nitrogen, and was then charged with CuI (0.074 g, 0.39 mmoL, 0.5 eq), **L2** (0.076 g, 0.39 mmoL, 0.5 eq) and Cs_2CO_3 (0.63 g, 2.0 mmoL, 2.5 eq), followed by addition of DMF (2 mL). The solution was stirred for 10 min at rt until reaction turn light green color. The appropriate substrate phenol (0.073 g, 0.78 mmoL, 1 eq) was added to the reaction mixture and then stirred for additional 5 min at rt. Compound **4** (0.25 g, 0.78 mmoL, 1eq) was dissolved in minimum amount of solvent and then added into the reaction mixture. The reaction mixture was then heated from rt to between 50 and 75°C for 12–36 h depending on the substrate. The reaction mixture was cooled and then through pad of silica gel using ethyl acetate and hexane mixture (20:80, 100 mL) and then washed three times with the same solvent mixture (100 mL). The filtrate was washed with water (100 mL × 3) followed with brine (200 mL), dried using anhydrous sodium sulfate and concentrated *in vacuo* to yield brown oil. The crude oil was then purified by silica gel column chromatography using 100% hexane to afford **5** as white crystals. (0.18 g, 70%): mp 60–63°C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.59–7.54 (m, 4H, HAr), 7.47–7.40 (m, 2H, HAr), 7.37–7.31 (m, 1H, HAr), 7.16–7.03 (m, 7H), 6.92 (s, 2H, HC = CH); ^{13}C NMR (75 MHz, $CDCl_3$): 157.6, 157.2, 140.4, 135.8, 134.9, 134.6, 129.7, 128.8, 128.4, 127.0, 126.9, 122.7, 116.0, 115.8; IR (cm^{-1}): 3061, 2962, 2870, 1606, 1510, 1485, 1419, 1365, 1230, 1183, 1174, 1124, 1105, 1006, 896, 836, 728; HRMS (ESI), calculated for $C_{20}H_{16}O_2$ $[M\text{-}H]^-$ 287.1072; found 287.1053; HPLC analysis: 91% purity.

General procedure for coupling reactions using trans-N-(2-pyridylmethylene)aniline (L1): (E)-4-((2-(4-(Tert-butyl)phenoxy) vinyl)oxy)-1,1′-biphenyl (6). An oven dried, three-necked, round-bottomed flask (50 mL) equipped with a nitrogen inlet, reflux condenser, rubber septum was repeatedly evacuated and back-filled with dry and pure nitrogen, and was then charged with CuI (0.095 g, 0.5 mmoL), **L1** (0.09 g, 0.5 mmol), *tert*-butyl phenol (0.18 g 1.2 mmoL) and Cs_2CO_3 (0.81 g, 2.5 mmoL), followed by the addition of anhydrous and degassed acetonitrile (1.2 mL). The flask was evacuated and back-filled with nitrogen and compound **4** (0.32 g, 1 mmoL) added at rt. The reaction mixture was stirred and heated to the required temperature of 80°C for the 48 h. After cooling to rt, the mixture was diluted with dichloromethane (20 mL) and filtered through a plug of celite, with the filter cake being further washed with dichloromethane (10 mL). The filtrate was washed with saturated NH_4Cl (15 mL), and twice with water (10 mL). The collected aqueous phases were extracted twice with dichloromethane (10 mL). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield brown solid. The crude product was fixed with 6 g silica gel and then purified using silica gel chromatography (100% hexane) to afford **6** a white solid (0.20 g 65%): mp 59–62°C. ^{1}H NMR (300 MHz, $CDCl_3$) 7.59–7.52 (m, 4H, HAr), 7.46–7.40 (m, 2H, HAr), 7.38–7.33 (m, 3H, HAr), 7.15–7.09 (d, 2H, J = 8.5 Hz, HAr), 7.02–6.97 (d, 2H, J = 8.6 Hz), 6.91 (s, 2H, CH = CH), 1.32 (s, 9H, 3 x $–CH_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 157.2, 155.3, 145.6, 140.6, 135.7, 135.3, 134.2, 128.8, 128.4, 127.0, 126.8, 126.5, 116.0, 115.3, 34.3, 31.5 ppm; IR (cm^{-1}): 3052, 2961, 2931, 2867, 1607, 1512, 1487, 1367, 1298, 1229, 1187, 1127, 1105, 1079, 1006, 839, 723; HRMS(ESI), calculated for $C_{24}H_{24}O_2$ $[M+H]^+$ 345.1854; found 345.1849; elemental analysis calculated for $C_{24}H_{24}O_2.1.25H_2O$: C, 78.55; H, 7.01; found: C, 78.55; H, 7.27.

(E)-4-[2-(4-Methoxyphenoxy)vinyloxy]biphenyl (7). Compound **7** was prepared according to the general method described for compound **6** elsewhere, employing **4** (0.2 g, 0.62 mmoL, 1 eq) and 4-methoxyphenol (0.077 g, 0.62 mmoL, 1 eq), Cs_2CO_3 (0.50 g, 1.6 mmoL, 2.5 eq), CuI (0.59 g, 0.31 mmoL, 0.5 eq) and **L1** (0.057 g, 0.31 mmoL, 0.5 eq) heating the reaction mixture at 80°C for 48 h to furnish the crude product, which was purified by column chromatography using hexane as the eluent to afford **7** as white crystals (40 mg, 40%): mp 112–115°C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.61–7.52 (m, 4H, HAr), 7.47–7.40 (m, 2H, HAr), 7.36–7.30 (m, 1H, HAr), 7.10 (d, 2H, J = 8.6 Hz), 7.00 (d, 2H, J = 9.0 Hz), 6.91–6.84 (m, 4H, HAr and HC(O) = C(O)H), 3.80 (s, 3H, $–CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 156.3, 154.3, 150.5, 139.5, 135.6, 135.1, 132.7, 131.4, 129.0, 127.8, 127.3, 125.8, 116.1, 115.0, 113.8, 54.7 ppm; IR(cm^{-1}): 3059, 1658, 1605, 1517, 1485, 1420, 1319, 1264, 1226, 1173, 1122, 896, 838, 737, 639; HRMS(ESI), calculated for $C_{21}H_{18}O_3$ $[M\text{-}H]^-$ 317.1178; found 317.1158; HPLC analysis: 92% purity.

(E)-(2-([1,1′-Biphenyl]-4-yloxy)vinyl)(phenyl)sulfane (8). The compound **8** was prepared according to the general procedure described for the compound **6** elsewhere employing **4** (0.15g, 0.47 mmoL, 1 eq) and thiophenol (0.051g, 0.05 mL, 0.47 mmoL, 1 eq), Cs_2CO_3 (0.38 g, 1.2 mmoL, 2.6 eq), CuI (0.044 g, 0.23 mmoL, 0.49 eq) and **L1** (0.042 g, 0.23 mmoL, 0.49 eq) heating the reaction mixture at 60°C for 10 h to give crude product, which was purified using silica gel column chromatography (100% hexane) to give compound **8**, as white crystals (0.12 g, 90%). (When a mixture of *Z* and *E*-**4** [1:9] was used as the starting material under same conditions at a temperature above 100°C afforded a mixture of *Z* and *E*-**8** [1:9]. They were distinguished from each other by their coupling constants. J_{cis} = 5.7 Hz, whereas J_{trans} = 12 Hz (^{1}H-NMR data of these mixtures are found elsewhere.) The characterization data below is that of **8** obtained from the reaction **4** with thiophenol: mp 92–96°C. ^{1}H NMR (300 MHz, CD_2Cl_2): 7.66–7.54 (m, 4H, HAr), 7.48–7.40 (m, 2H, HAr), 7.37–7.28 (br s, 6H, HAr), 7.20–7.09 (m, 3H, HAr), 6.09–6.10 (d, 2H CH = CH, J = 12.0 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): 155.9, 150.6, 140.3, 137.5, 137.1, 128.9, 128.8, 128.5, 127.2, 127.0, 126.9, 125.7, 117.4, 102.1; IR(cm^{-1}): 3054, 2985, 1659, 1624, 1599, 1515, 1485, 1265, 1233, 1185, 1174, 1112, 1086, 1025, 1007, 924, 839, 739, 407; HRMS (ESI) calculated for $C_{20}H_{16}OS[M+H]^+$ 305.1000; found 305.0998; elemental analysis calculated for $C_{20}H_{16}OS$. 0.11 H_2O: C, 78.40; H, 5.34; found: C, 78.40; H, 5.29.

(E)-1-(2-([1,1′-Biphenyl]-4-yloxy)vinyl)-1H-indole (9). The compound **9** was prepared following the procedure described for **5** with **4** (0.32 g, 1 mmoL, 1 eq), indole (0.14 g, 1.2 mmoL, 1.2 eq), Cs_2CO_3 (0.81 g, 2.5 mmoL, 2.5 eq), CuI (0.095 g, 0.5 mmoL, 0.5 eq) and **L2** (0.097 g, 0.5 mmoL, 0.5 eq) at 70°C for 12 h to give crude products, which were purified by silica gel column chromatography using ethyl acetate-hexane (9:95) to afford compound **9** as white crystals (0.27 g, 87%): mp 140–142°C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.58–7.46 (m, 6H, HAr), 7.40–7.32 (m, 3H, HAr), 7.25–7.21 (m, 1H, HAr), 7.20–7.14 (m, 2H, HAr), 7.12–7.02 (m, 4H, HAr and H(O)C = (N)CH), 6.55 (d, H, J = 3.1 Hz, HAr). ^{13}C NMR (75 MHz, $CDCl_3$): 156.8, 140.4, 136.5, 136.4, 128.9, 128.8, 128.5, 127.1, 126.9, 125.7, 125.6, 121.2, 120.5,

116.5, 115.2, 109.8, 104.0 ppm; IR (cm^{-1}): 3034, 2358, 2338, 1682, 1606, 1515, 1485, 1475, 1462, 1358, 1333, 1322, 1301, 1232, 1202, 1186, 1174, 1134, 1115, 1088, 1031, 1007, 907, 865, 834; HRMS (ESI), calculated for $C_{22}H_{17}NO$ $[M+H]^+$ 312.1388; found 312.1381; elemental analysis calculated for $C_{22}H_{17}NO.0.25H_2O$: C, 83.65; H, 5.58; N, 4.43; found: C, 83.61; H, 5.65; N, 4.01.

(E)-1-[2-(Biphenyl-4-yloxyl)vinyl]-1H pyrrole (10). The compound **10** was prepared following the procedure described for **5** with **4** (0.2 g, 0.62 mmoL, 1 eq), pyrrole (0.062 g, 0.93 mmoL, 1.5 eq), Cs_2CO_3 (0.40 g, 1.2 mmoL, 2.5 eq), CuI (0.059 g, 0.31 mmoL, 0.5 eq) and **L2** (0.060 g, 0.31 mmoL, 0.5 eq) at 70°C for 12 h to give crude products, which were purified by silica gel column chromatography using ethyl acetate-hexane (9:95) to afford compound **10** as white crystals (0.14 g, 85%): mp 102–105°C. Olefinic protons coupling on the named compound gave an AB system with a typical roof effect with peaks centered at 7.04 and 6.99 ppm. ^{1}H NMR (300 MHz, $CDCl_3$): 7.62–7.53 (m, 4H, HAr), 7.48–7.40 (m, 2H, HAr), 7.38–7.31 (m, 1H, HAr), 7.17–7.09 (m, 2H, HAr), 7.04 (distorted d, 1H, J = 11.1 Hz, (O)-CH=CH(N)), 6.99 (distorted d, 1H, J = 11.1 Hz, (O)-CH=CH(N)), 6.82 (dd, 2H, J_1 = 4.2 Hz, J_2 = 2.2 Hz, CH=CH of pyrrole), 6.28 (dd, 2H, J_1 = 4.2 Hz, J_2 = 2.2 Hz, CH=CH); ^{13}C NMR (75 MHz, $CDCl_3$): 156.8, 140.4, 136.3, 135.0, 128.8, 128.4, 127.1, 126.9, 119.6, 118.3, 116.5, 110.0 ppm; IR (cm^{-1}): 3086, 3034, 2715, 2682, 1659, 1607, 1587, 1517, 1485, 1360, 1326, 1300, 1239, 1229, 1185, 1173, 1119, 1094, 1072, 1056, 1007, 975, 907, 857, 838, 614; HRMS (ESI) calculated for $C_{18}H_{15}NO$ $[M+H]^+$ 262.1232; found 262.1233; elemental analysis calculated for $C_{18}H_{15}NO.0.17H_2O$: C, 81.77; H 5.85; N, 5.29; found: C, 81.76; H, 5.91; N, 5.03.

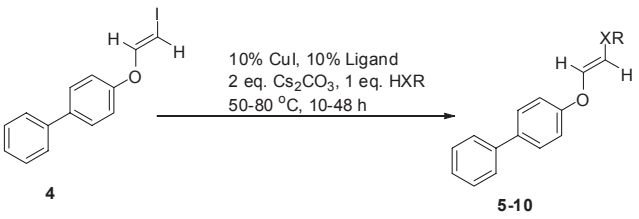
General photooxidation procedure. In a NMR tube, an olefin (0.0048 mmoL) was dissolved in $CDCl_3$ (0.5 mL). The photosensitizer [5-(4-methoxyphenyl)-10,15,20-triphenyl-21-23-dithiaporphyrin, CMP-OMe, 3 mg, 0.0048 mmoL] was added to this solution. The reaction mixture was irradiated for 15 min using a diode laser (690 nm, 200 mW cm^{-2}). The reaction of olefins with singlet oxygen was monitored by the decrease of olefinic peaks in ^{1}H-NMR spectra. The formation of photooxidation products were also determined by appearance of the formate (or thioformate) peaks in ^{1}H-NMR spectra.

RESULTS AND DISCUSSION

For the synthesis of the 1,2-diheteroatom-substituted olefins, a four-step scheme was developed where 4-phenylphenol **1** was used in one side. First, 4-phenylphenol was vinylated using 1,1,2-trichloroethylene (27) to give the corresponding 4-((1,2-dichlorovinyl)oxy)-1,1′-biphenyl **2** with yield of more than 85% (28,29). 4-(ethynyloxy)-1,1′-biphenyl **3** was prepared by elimination reaction using *n*-BuLi in 70% yield (28,29). Although **1** was used in this article, other types of alcohols and phenols can also be converted to the alkyne form (28). Hydrozirconation and iodinolysis of **3** led to 2-iodoenol ether **4** in 55% yield (30,31). Using the copper-catalyzed coupling reaction, **4** were linked with various substrates bearing the different functional groups (16,32,33).

The reaction with thiophenol gave the best yield (**8**: 90%) and short reaction time followed by reactions with aromatic amines (**9**: 87%, **10**: 85%) and least yield by the reaction with phenols (compounds **5**, **6** and **7**). The trend could be explained by the relative nucleophilicity of the substracts (–SH > –NH > –OH; Table 1). Two coupling conditions were used; either trans-*N*-(2-pyridylmethylene)aniline as ligand in acetonitrile as solvent (16,34) or 2-pyridin-2-yl-benzoimidazole as ligand in DMF as solvent (33). For the compound **5**, slightly better yields were obtained using the latter coupling condition and the reaction time was reduced to 16 h compared to the former condition (36 h). To test the robustness of our method, some selected analogs of the phenolic and azole derivatives were synthesized. Phenolic derivatives required high temperatures of 70–80°C for 16–48 h of reaction time and yields were poor–good (40–70%). Further optimization of reaction conditions for these low yielding coupling reactions will be pursued. Reaction with the azole derivatives required low temperatures between 50 and 75°C and shorter reaction time, 12 h. The yields for **9** and **10** were very good (87% and 85% respectively). Our methodology encountered, however, a limitation in the case of aniline. Coupling using aniline substrate gave an extremely low yield that the product could not be isolated. In all of these reactions, the products gave single isomers (*E*-1,2-diheteroatom-substituted olefins) as only the **4** was used for the coupling (33). This is a well-known Ullmann-type coupling reaction, which proceed in stereospecific fashion (32,33). The stereospecificity of the reaction was also supported by the fact that a mixture of *E/Z*-**4** (9:1) at >100°C gave a mixture of *E/Z*-**8** at the same ratio of 9:1 (NMR Data S1, Supporting Information).

Table 1. Copper-catalyzed vinylation of nucleophiles.



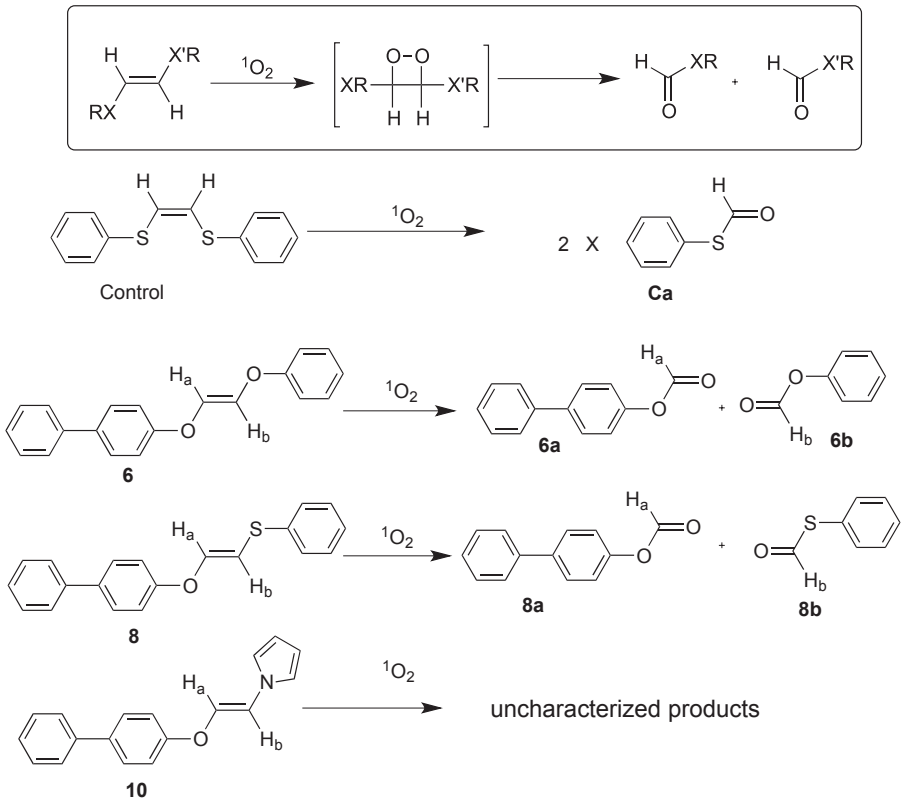
4 5-10

Product	Substrate (HXR)	Ligand [rx. temp (°C), time (h)]	Yield (%)
5		L1[a] (75, 36) L2[b] (75, 16)	65 70
6		L1 (80, 48)	65
7		L1 (80, 48)	40
8		L1 (60, 10)	90
9		L2 (70, 12)	87
10		L2 (65, 12)	85

[a] L1 = *trans-N*-(2-pyridylmethylene)aniline.
[b] L2 = 2-pyridin-2-yl-benzoimidazole.

Unlike typical coupling constants of 12–18 Hz for protons at *E*-olefins and 6–12 Hz at *Z*-counterparts, the coupling constants of the hydrogen atoms on 1,2-diheteroatom-substituted olefins were found to be reduced and in some cases even to zero. Only a peak was observed from 1,2-diaryloxyalkenes (**5, 6** and **7**) where the two olefinic protons are in very similar environment. On the other hand, whereas **8** showed doublet peaks, **10** showed distorted doublet peaks (AB system): *E*-**8** (J = 12 Hz), *Z*-**8** (J = 5.3 Hz), *E*-**10** (J = 11.1 Hz). Such unusual small coupling constants of olefins were also observed in monohetereoatom-substituted olefins, especially the oxygen-substituted olefins (16,32,33).

To examine the oxidation rate of these electron-rich alkenes with singlet oxygen (Scheme 2), we irradiated compounds **6**, **8** and **10** in the presence of 5-(4-methoxyphenyl)-10,15,20-triphenyl-21,23-dithiaporphyrin as a photosensitizer (35). All experiments were carried out following the standard procedure



Scheme 2. Possible [2 + 2] addition reaction of electron-rich olefins with singlet oxygen and expected products of control, **6**, **8** and **10**.

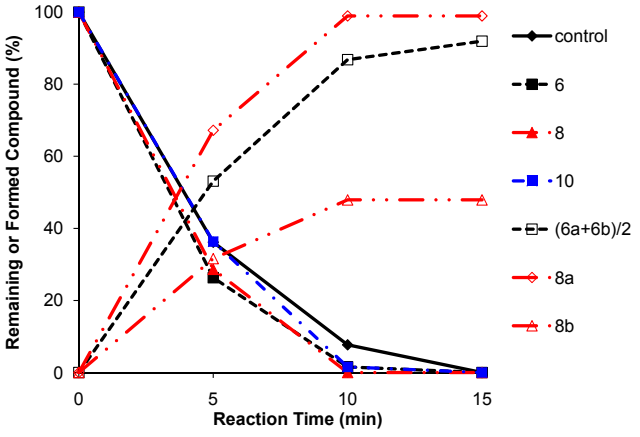


Figure 1. Photooxidation of olefins (**6**, **8** and **10**) by the irradiation of 690 nm diode laser at 200 mW cm^{-2} with a photosensitizer (CMP-OMe) in chloroform-d_3.

previously set by our group with a slight modification using a 690 nm diode laser source (200 mW cm^{-2}; 14). In our experiments, the amount of sensitizer used was not catalytic. Herein, the ratio of olefin and photosensitizer used was 1:1 to mimic the situation of prodrug where the olefinic linker could be used for connecting one drug molecule to one photosensitizer molecule (14,15). The reaction solutions were irradiated for 15 min and monitored every 5 min using olefinic peaks in ^{1}H-NMR each time to monitor the progress of the reactions. Upon the oxidation by singlet oxygen, the olefinic peaks decreased.

Table 2. Time-dependent decrease of the olefins and formation of photoproducts.

Time (min)	Remaining olefins (%)				Observed product (%)			
	Control	6	8	10	Ca	(6a + b)/2*	8a	8b
0	100	100	100	100	0	0	0	0
5	38	26	29	27	0	53	67	32
10	11	2	0	0	1	87	99	48
15	0	0	0	0	2	92	99	48

*In ^{1}H-NMR, the formate peaks of expected products of 6 (6a and b) were too close to be distinguished. Thus, two peaks were integrated together and divided by 2.

(*Z*)-1,2-*Bis*(phenylthio)ethylene was used as a control against which the reaction rates were compared. Analysis of the data indicated that not much difference exists among these linkers with respect to their rate of reaction with singlet oxygen (Fig. 1 and Table 2). Double bond peaks of all four substrates disappeared within 15 min of the irradiation. The fast reaction of **6** (1,2-diaryloxyalkene) and **8** (1-aryloxy-2-arythio-alkene) is consistent with our previous report (14). The cleaved formate products **6a**, **b** and **8a** were formed consistent with the decrease of the olefins **6** and **8** (Table 2). On the other hand, cleaved thioformate products **8b** was formed much less (about half) than oxidized olefin **8** presumably due in part to the oxidation of sulfur atom (14,36) and/or cleavage of carbon-sulfur bond (37). In the case of the control, we also detected diphenyl disulfide after the photooxidation. The fast reaction of **10** (1-

aryloxy-2-amino-alkene) with singlet oxygen was also observed. The olefinic peaks of **10** completely disappeared in 10 min. In addition, we also observed the decrease of the peaks of protons at the pyrrole ring at a little bit slower rate: 73% (olefinic proton) *vs* 60% (protons at the pyrrole ring) reduction after 5 min. One notable observation is that the formate product was not detected in the ^{1}H-NMR from the oxidation of **10**. Photooxidation of pyrrole ring of **10** could produce many possible photoproducts (38). Further investigation is needed to reveal the detailed mechanism of oxidation of **10**.

CONCLUSION

In summary, a facile and versatile synthesis of *E*-1,2-diheteroatom-substituted electron-rich alkenes was established. Not only symmetric vinyl diethers but also unsymmetrically heteroatom-substituted olefins could be prepared using phenols, thiols and *N*-heterocycles with high stereospecificity. In addition to 1,2-diaryloxyalkene and 1-aryloxy-2-arylthio-alkene, 1-aryloxy-2-amino-alkene also react with singlet oxygen.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Table of contents.

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