$VO(acac)_2$-Catalyzed Oxidative Coupling Reactions of Phosphonium Salts

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Abstract: A novel eco-safer protocol for the preparation of symmetric or unsymmetric olefins directly from phosphonium salts under oxygen atmosphere in the presence of $VO(acac)_2$ (1.0 mol%) was developed.

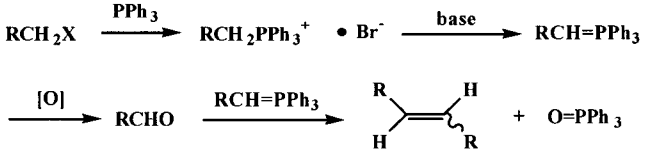
Introduction

The oxidative coupling reaction of phosphorus ylides to produce symmetric olefins was first investigated by Bestmann[1,2] and co-workers many years ago. Since then, many[3,4,5] modifications or improvements have been reported in the literature (Scheme 1). The oxidants used so far in this reaction include molecular oxygen,[1] $NaIO_4$,[2] $(PhO)_3PO_3$,[3] or *N*-camphorsulfonyloxaziridine.[4] Although the potential usefulness of such couplings can be clearly sensed through the classic examples such as preparation[6] of carotene from vitamin A, further application of this reaction appears to have been seriously obstructed by the difficulties imposed by the oxidants so far employed. For example, when $NaIO_4$ is used as the oxidant,[2] the ylides must be converted to the corresponding IO_4^- salts, which tend to explode upon heating. As a consequence, the procedure becomes not only intricate but also dangerous in some cases. The other oxidants are either very expensive (e.g., *N*-camphorsulfonyloxaziridine) or inconvenient [$(PhO)_3PO_3$ decomposing to O_2 and triphenyl phosphate at temperatures above −35 °C]. The requirement of using excess oxidant is also a problem, because the residual oxidant renders the separation process rather complicated. Molecular oxygen seems to be a superior oxidant since it is cheap and creates no separation difficulty during the workup. However, until now with molecular oxygen as the oxidant, the reaction was either very slow or did not occur at all.[1]

Results and Discussion

In efforts to explore a more facile and eco-safe protocol for the synthesis of symmetric olefins via oxidative coupling reactions of ylides generated in situ from the corresponding phosphonium salts, we found that under an oxygen atmosphere, a catalytic amount of $VO(acac)_2$ (0.01 equiv) can significantly speed up the oxidative coupling reactions of ylides (generated in situ) to give the corresponding symmetric olefins in excellent yields. A $VO(acac)_2/O_2$ system has been used[7] in many oxidation reactions. However, to the best of our knowledge, it has not been used in oxidative coupling reactions of phosphorus ylides.

Scheme 1



Our synthetic method is illustrated in Scheme 2. This is a biphasic reaction system (solid/liquid: $PhMe/K_2CO_3$) with 18-crown-6 (0.01 equiv) as the phase transfer catalyst (PTC) and the phosphonium salt derived from benzyl bromide and triphenylphosphine as the substrate (Method A). At 60 °C, part of the ylide was oxidized to the corresponding aldehyde by O_2 in the presence of $VO(acac)_2$ (0.01 equiv). The intermediate aldehyde then reacts with the remaining starting ylide to give the symmetric olefin in 94% yield.

It is known[8] that ylides can be generated in biphasic systems (water/organic phase) under phase transfer conditions. Therefore, we next examined a liquid/liquid biphasic reaction system (40% NaOH aqueous solution/CH_2Cl_2) using $n\text{-}Bu_4N^+Br^-$ as a phase transfer catalyst. We found that the ylide was indeed formed, although the overall yield of the coupling product was very low (<5%), presumably due to rapid hydrolysis of the intermediate ylide.[8] An apparent advantage of this new procedure (Method A) is that the use of strong bases such as butyllithium or sodium amide under strict anhydrous reaction conditions is avoided.[4]

Other metal catalysts, which have been used very often in oxidation under an oxygen atmosphere, were also examined under the same conditions. The results are summarized in Table 1. The results with other phosphonium salts under the optimized reaction conditions are shown in Table 2. We found that, for phosphonium salts having an electron-withdrawing or weak electron-donating group on the phenyl ring, the oxidative coupling reactions proceeded very well, giving the corresponding symmetric olefins in good yields. However, other phosphonium salts generally gave low yields of products (3−5%) under the same conditions. For example, if the Wittig salts have a strong electron-donating group on the phenyl ring, the generated ylides were easily oxidized to give very complicated products at 60−70 °C, while at room temperature, no reactions occurred.

Having found that K_2CO_3 as a base was not strong enough to generate ylide at room temperature, we then utilized a stronger base (^{t}BuOK) and carried out the reaction at room temperature in dichloromethane (Scheme 3, Method B). The results were very gratifying. The reactions now proceeded smoothly to give the correspond-

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(1) Bestmann, H. J.; Kratzer, O. *Chem. Ber.* **1963**, *96*, 1899.
(2) Bestmann, H. J.; Armsen, R.; Wagner, H. *Chem. Ber.* **1969**, *102*, 2259.
(3) Bestmann, H. J.; Kisielowski, L.; Distler, W. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 298.
(4) Davis, F. A.; Chen, B.-C. *J. Org. Chem.* **1990**, *55*, 360.
(5) Kiselyov, A. S. *Tetrahedron Lett.* **1994**, *48*, 8951.
(6) Bestmann, H. J.; Kratzer, O.; Armsen, R. *Liebigs. Ann. Chem.* **1973**, 760.
(7) Hirao, T. *Chem. Rev.* **1997**, *97*, 2707.
(8) ApSimon, J. W.; Dixit, D. M. *Synth. Comm.* **1982**, *12*, 113.

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Scheme 2

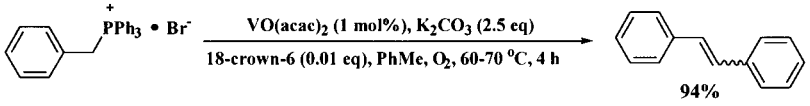
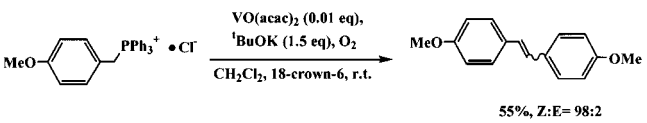


Table 1. Effect of Various Metal Catalysts in the Oxidative Coupling Reactions of Phosphonium Salts

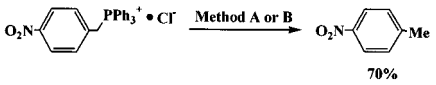
catalysts	yield/%[a]
none	31
$VO(acac)_2$	94
MnO_2	20
$Co(acac)_2$	50
$Mn(acac)_3$	40
$Ni(acac)_2$	50

[a] Isolated yields.

Scheme 3



Scheme 4

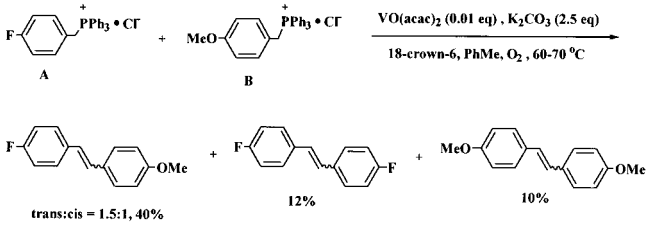


ing symmetric olefins in high yields (Scheme 3, Table 2, entries 5 and 6). Under such conditions, unstabilized ylides also underwent the expected coupling reaction, affording the symmetric olefins in good yields with preferential *Z*-configuration (98:2% or >98:<2%) (Table 2, entries 7 and 8). The *p*-nitrobenzylphosphonium chloride and the stablized ylide prepared from bromoacetone with triphenylphosphine seem to be exceptions, because the former only yields *p*-nitrotoluene (Scheme 4), whereas the latter did not react at all under the conditions employed in Method A or B (Table 2, entry 10). We believe that *p*-nitrotoluene is derived from the hydrolysis (Method A) and alcoholysis (Method B) of the corresponding ylide generated in situ.[9] It is noted that the *Z*/*E* ratios of the resulting olefins are generally the same as those under the typical Wittig conditions.[10a,b]

We also investigated the oxidative cross-coupling reaction between different phosphonium salts. In most cases, the cross-coupling products could be isolated, but the yields were not so high because the self-coupling reactions were unavoidable. However, some selectivity was still observed in some cases. For example, the ylide generated from Wittig salt B was more easily oxidized to the corresponding aldehyde due to the electron-donating group on the phenyl ring and the ylide generated from Wittig salts A was relatively more stable to the oxidation. In such a case, the cross-coupling product was the major product (Scheme 5).

In conclusion, we have developed a novel, useful, practical, and eco-safe protocol for the preparation of symmetric or unsymmetric olefins from semistabilized or nonstabilized ylides under an oxygen atmosphere in the presence of $VO(acac)_2$. On the basis of the conditions employed, this oxidative coupling method has great potential in industrial applications. Efforts to elucidate the scope and limitations of this oxidation system are underway.

Scheme 5



Experimental Section

General. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI methods, and HRMS was measured on a Finnigan MA+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. All solid compounds gave satisfactory CHN microanalyses. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out on 300−400 mesh silica gel under slightly elevated pressures.

Typical Procedure for the Preparation of Phosphonium Salts. The bromides or chlorides (0.05 mol) and triphenylphosphine (0.05 mol) were added into dry toluene (20 mL). The resulting mixture was stirred under reflux for 8 h. After the mixture was cooled, the precipitates were collected by filtration, washed with toluene and ether, and dried in vacuo. The product was used for the next reaction without recrystallization.

Typical Procedure for the Oxidative Coupling Reaction. Method A: The phosphonium salt (1.0 mmol), $VO(acac)_2$ (0.01 mmol), crown ether (0.01 mmol), and K_2CO_3 (2.5 mmol) were added into toluene (10 mL). The resulting mixture was stirred under an oxygen atmosphere at 60−70 °C for 8 h. After the mixture was cooled, the precipitates were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography.

Method B. The phosphonium salt (1.0 mmol), $VO(acac)_2$ (0.01 mmol), crown ether (0.01 mmol), and ^{t}BuOK (1.5 mmol) were added into CH_2Cl_2 (10 mL), and the reaction mixture was stirred under an oxygen atmosphere at room temperature for 8 h. The reaction mixture was washed with water and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was separated by flash column chromatography.

Method C: Typical Cross-Coupling Reaction Procedure. The Wittig salts A (0.5 mmol) and B (0.5 mmol), $VO(acac)_2$ (0.01 mmol), crown ether (0.01 mmol), and ^{t}BuOK (1.5 mmol) were added into anhydrous CH_2Cl_2, and the reaction mixture was stirred under an oxygen atmosphere at room temperature for 8 h. The reaction mixture was washed with water and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was separated by flash column chromatography.

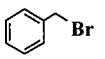
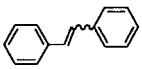
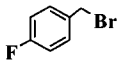
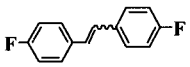
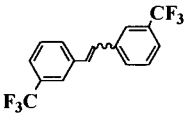
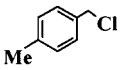
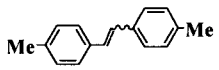
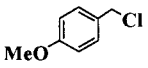
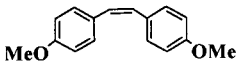
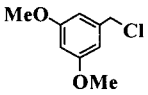
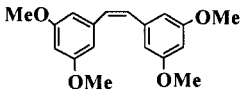
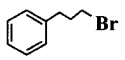
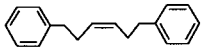
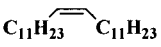
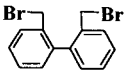
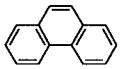
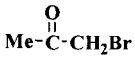
Preparation of Stilbene (Table 2, Entry 1). Stilbene was prepared according to Method A (eluent: petroleum ether): cis: trans = 1.7:1; total yield = 94%. **Trans isomer**: 30 mg, colorless solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (s, 2H), 7.21−7.30 (m, 4H), 7.31−7.39 (m, 4H), 7.45−7.55 (m, 2H). The ^1H NMR spectral data were consistent with those of an authentic sample.[1] **Cis isomer**: 52 mg, colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.60 (s, 2H), 7.10−7.30 (m, 10H). The ^1H NMR spectral data were consistent with those of an authentic sample.[1]

Preparation of 4,4′-Difluorostilbene (Table 2, Entry 2). 4−4′-Difluorostilbene was prepared according to Method A

(9) (a) VanderWerf; C. A.; McEwen, W. E.; Zanger, M. *J. Am. Chem. Soc.* **1959**, *81*, 3806. (b) Grayson, M.; Keough, P. T. *J. Am. Chem. Soc.* **1960**, *82*, 3919.

(10) (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Bellucci, G.; Chiappe, C.; Moro, G. L. *Tetrahedron Lett.* **1996**, *37*, 4225.

Table 2. Oxidative Coupling Reaction of Phosphonium Salts

entry	halides	products	reaction condtion	yield/%[a]	Z/E
1			A[b]	93	1.7:1
2			A	83	1.6:1
3			A	84	1.3:1
4			A	75	1.3:1
5			B[c]	55	98:2
6			B	51	>98:<2
7			B	78	98:2
8	$n\text{-}C_{12}H_{25}Br$		B	62	>98:<2
9			A	70	---
10		no reaction	A or B	—	---

[a] Isolated yields. [b] Method A: PhMe, K_2CO_3 (2.5 equiv), 18-crown-6 (0.01 equiv), O_2 atmosphere, $VO(acac)_2$ (0.01 equiv), at 60−70 °C. [c] Method B: CH_2Cl_2, ^tBuOK (1.5 equiv), 18-crown-6 (0.01 equiv), O_2 atmosphere, $VO(acac)_2$ (0.01 equiv), at room temperature.

(eluent: petroleum ether): cis:trans = 1.56:1; total yield = 83%. **Trans isomer**: 35 mg, 32%, colorless solid; mp 148−151 °C; IR (KBr) *v* 2854, 1682, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 2H), 7.02−7.07 (m, 4H), 7.43−7.48 (m, 4H); MS (EI) *m*/*z* 216 (M^+), 195, 183. Found: C, 60.95%; H, 3.26%. Calcd for $C_{14}H_{10}F_2$: C, 60.77%; H, 3.19%. **Cis isomer**: 53 mg, 51%, colorless oil; IR (neat) *v* 2854, 1682, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.51 (s, 2H), 6.89−6.94 (m, 4H), 7.15−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.34 (d, J_{C-F} = 22.3 Hz), 129.04 (d, J_{C-F} = 1.2 Hz), 130.40 (d, J_{C-F} = 10.3 Hz), 132.90 (d, J_{C-F} = 3.5 Hz), 161.8 (d, J_{C-F} = 245.2 Hz); MS (EI) *m*/*z* 216 (M^+), 195, 183; HRMS calcd for $C_{14}H_{10}F_2$ (M) 216.0751, found 216.0755.

Preparation of 3,3′-Trifluoromethylstilbene (Table 2, Entry 3). 3,3′-Trifluoromethylstilbene was prepared according to Method A (eluent: petroleum ether): cis:trans = 1.3:1; total yield = 82%. **Trans isomer:** 55 mg, 35%, colorless solid; mp 120−122 °C; IR (KBr) *v* 2842, 1334, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19 (s, 2H), 7.47−7.57 (m, 4H), 7.68−7.78 (m, 4H); MS (EI) *m*/*z* 316 (M^+), 297, 247. Found: C, 60.95%; H, 3.26%. Calcd for $C_{16}H_{10}F_6$: C, 60.77%; H, 3.19%. **Cis isomer:** 73 mg, 46%, colorless oil; IR (neat) *v* 2842, 1442, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.71 (s, 2H), 7.26−7.40 (m, 4H), 7.46−7.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 123.20 (q, J_{C-F} = 7.0 Hz), 124.0 (q, J_{C-F} = 270.9 Hz), 124.53 (q, J_{C-F} = 4.0 Hz), 128.87, 129.20, 129.70 (q, J_{C-F} = 1.1 Hz), 131.20 (q, J_{C-F} = 32.2 Hz), 137.41; MS (EI) *m*/*z* 316 (M^+), 297, 247; HRMS calcd for $C_{16}H_{10}F_6$ (M) 316.0687; found 316.0681.

Preparation of 4,4′-Dimethylstilbene (Table 2, Entry 4). 4,4′-Dimethylstilbene was prepared according to Method A (eluent: petroleum ether): cis:trans = 1.3:1; total yield = 75%. **Trans isomer:** 33 mg, 32%, colorless solid; mp 130−132 °C; IR (KBr) *v* 3019, 1512, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 6H), 7.02 (s, 2H), 7.10−7.14 (m, 4H), 7.36−7.40 (m, 4H); MS (EI) *m*/*z* 208 (M^+), 193, 178. Found: C, 91.95%; H, 7.57%. Calcd for $C_{16}H_{16}$: C, 92.26%; H, 7.57%. **Cis isomer**: 43 mg, 43%, colorless liquid; IR (neat) *v* 2854, 1682, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 6H), 6.51 (s, 2H), 6.90−6.94 (m, 4H), 7.20−7.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.22, 128.71, 128.87, 129.50, 134.48, 136.70; MS (EI) *m*/*z* 206 (M^+), 193, 178; HRMS calcd for $C_{16}H_{16}$ (M) 208.1252, found 208.1259.

Preparation of 4,4′-Dimethoxylstilbene (Table 2, Entry 5). 4,4′-Dimethoxylstilbene was prepared according to Method B (eluent: petroleum ether: AcOEt = 10:1). **Cis isomer**: 114 mg, 55%, colorless oil; IR (neat) *v* 2838, 1606, 1506 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 6H), 6.87−6.90 (m, 4H), 6.94 (s, 2H), 7.42−7.46 (m, 4H); MS (EI) *m*/*z* 240 (M^+), 225, 165; HRMS calcd for $C_{16}H_{16}O_2$ (M) 240.1150, found 240.1151. The ^1H NMR spectral data were consistent with those of an authentic sample.[1]

Preparation of 3,3′,5,5′-Tetramethoxylstilbene (Table 2, Entry 6). 3,3′,5,5′-Tetramethoxylstilbene was prepared according to Method B (eluent: petroleum ether: AcOEt = 10:1). **Cis isomer**: 76 mg, 51%, colorless oil; IR (neat) *v* 2938, 2836, 1590, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.58 (s, 12H), 6.22−6.23 (m, 2H), 6.35−6.37 (m, 4H), 6.45 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.48, 99.84, 107.20, 130.49, 138.93, 160.42; MS (EI) *m*/*z* 300 (M^+), 269, 182; HRMS calcd for $C_{18}H_{40}O_4$ (M) 300.1361, found 300.1342.

Preparation of $C_{24}H_{48}$ (Table 2, Entry 8). This compound was prepared according to Method B (eluent: petroleum ether). ^{1}H NMR spectral data indicated no trans isomer. **Cis isomer**: 104 mg, 62%, colorless oil; IR (neat) ν 2924, 1465, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 8.0 Hz, 6H), 1.24−1.45 (m, 36H), 2.0−2.09 (m, 4H), 5.35−5.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.21, 22.82, 27.33, 29.46, 29.50, 29.70, 29.79, 29.83, 29.91, 32.06, 130.47; MS (EI) m/z 316 (M^+), 220, 205, 196; HRMS calcd for $C_{24}H_{48}$ (M) 336.3756, found 336.3757.

Preparation of 1,6-Diphenyl-3-hexene (Table 2, Entry 7). 1,6-Diphenyl-3-hexene was prepared according to Method A (eluent: petroleum ether). ^{1}H NMR spectral data indicated no trans isomer. **Cis isomer**: 94 mg, 81%, colorless oil; IR (neat) ν 3013, 2922, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.40−2.42 (m, 4H), 2.55−2.70 (m, 4H), 5.50−5.53 (m, 2H), 7.10−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.21, 35.79, 128.25, 128.31, 128.52, 129.47, 142.05; MS (EI) m/z 236 (M^+), 145, 91; HRMS calcd for $C_{18}H_{20}$ (M) 236.1565, found 236.1551.

Preparation of 4-Methoxyl-4′-fluorostilbene (Scheme 5). 4-Methoxyl-4′-fluorostilbene was prepared according to Method C (eluent: petroleum ether: AcOEt = 40:1): cis:trans = 1:1.5; total yield = 40%. **Trans isomer**: 27 mg, 24%, colorless oil; IR (neat) ν 2935, 1605, 1506 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 3H), 6.45 (d, J = 12.1 Hz, 1H), 6.53 (d, J = 12.1 Hz, 1H), 6.76−6.79 (m, 2H), 6.92−6.95 (m, 2H), 7.15−7.18 (m, 2H), 7.20−7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.26, 114.07, 115.52 (d, J_{C-F} = 22.2 Hz), 125.33, 127.58, 127.65, 127.87 (d, J_{C-F} = 20.2 Hz), 129.91, 133.75 (d, J_{C-F} = 3.5 Hz), 159.25, 162.40 (d, J_{C-F} = 245.2 Hz); MS (EI) m/z 228 (M^+), 213, 183, 165; HRMS calcd for $C_{15}H_{13}FO$ (M) 228.0950, found 228.0938. **Cis isomer**: 17 mg, 16%, colorless solid; mp 154−155 °C; IR (KBr) ν 2838, 1604, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3H), 6.89 (d, J = 8.1 Hz, 1H), 7.01−7.03 (m, 2H), 7.03−7.06 (m, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.44−7.47 (m, 4H); MS (EI) m/z 228 (M^+), 213, 183, 165. Found: C, 78.42%; H, 5.75%. Calcd for $C_{15}H_{13}FO$: C, 78.93%; H, 5.74%.

Preparation of Phenanthrene (Table 2, Entry 9). Phenanthrene was prepared according to Method A (eluent: petroleum ether): 124 mg, 70%, colorless solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59−7.70 (m, 6H), 7.89−7.92 (m, 2H), 8.70−8.73 (m, 2H). The ^{1}H NMR spectral data were consistent with those of an authentic sample.[2]

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Supporting Information Available: ^{1}H NMR charts and some ^{13}C NMR of symmetric olefins in Table 2 and unsymmetric olefins in Scheme 5. This material is available free of charge via the Internet at http://pubs.acs.org.

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