# Methylsulfonyl and Hydroxyl Substituents Induce *Z*-Stereocontrol in the McMurry Olefination Reaction

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**Abstract:** Aryl ketones possessing methylsulfonyl and hydroxyl substituents, that induce stereocontrol, selectively afford *Z*-olefins using a Zn–$TiCl_4$ catalyzed McMurry reaction.

**Key words:** McMurry olefination, stereocontrol, *Z*-olefins, acetylation

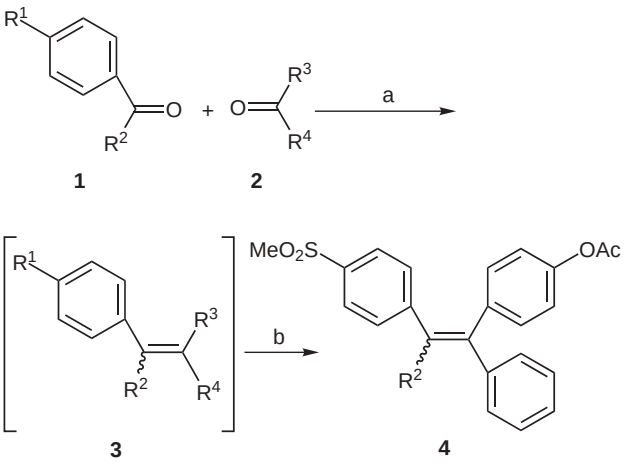
Condensation of carbonyl compounds as a method to synthesize olefins using the McMurry reaction is a useful transformation in organic synthesis.[1] In this regard, mechanistic aspects[2–5] of the McMurry reaction were studied in considerable detail. Coe and Scriven[6] reported a low valent titanium-mediated McMurry reaction which afforded (*Z*)-tamoxifen as the predominant stereoisomer (ratio *Z*:*E* = 9:1). Other studies subsequently showed that steric hindrance seems to be an important factor that affects the stereoselectivity of the McMurry reaction since deoxygenation of the pinacolic intermediate results in preferential formation of the olefin in which the bulkier and smaller substituents are *cis* to each other.[7] We now report a practical stereocontrol approach involving a McMurry reaction using functionalized aryl ketones that coordinate with metallic titanium to induce a high level of *Z*-selectivity.

As a part of our ongoing program to develop novel and highly selective COX-2 inhibitors,[8–10] we required a method to prepare (*Z*)-monoacetoxyphenyl analogs of the very potent and highly selective COX-2 inhibitor 1,1-diphenyl-2-(4-methylsulfonyl)hex-1-ene.[11] In this regard, carbonyl compounds **1** ($R^1$ = $SO_2Me$, $R^2$ = H, Me, Et, *n*-Pr, *n*-pentyl, *n*-hexyl, *n*-nonyl) required for these syntheses were prepared in 85–92% yield by oxidation of the respective methylthio compounds[11–13] using either MCPBA or Oxone®.[14]

The intermediate *Z*-olefin products **3** ($R^1$ = $SO_2Me$, $R^2$ = H, Me, Et, *n*-Pr, *n*-pentyl, *n*-hexyl, *n*-nonyl, $R^3$ = 4-hydroxyphenyl, $R^4$ = Ph) were generated in situ using a McMurry olefination reaction[15] by Zn–$TiCl_4$ catalyzed reductive cross-coupling of compounds **1** ($R^1$ = $SO_2Me$, $R^2$ = H, Me, Et, *n*-Pr, *n*-pentyl, *n*-hexyl, *n*-nonyl) with 4-hydroxybenzophenone (**2**, $R^3$ = 4-hydroxyphenyl, $R^4$ = Ph). Subsequent acetylation of intermediates **3**[16] afforded the target (*Z*)-acetoxyphenyl products **4** ($R^2$ = H, Me, Et, *n*-Pr, *n*-pentyl, *n*-hexyl, *n*-nonyl) in 63–72% overall yield (Scheme 1).[17]

Accordingly, we are pleased to report that the cross-coupling reaction of two aryl ketones functionalized by a sulfonyl and a hydroxyl group, proceeds in a stereocontrolled manner to afford the target *Z*-olefinic products **4** (Table 1). The structure of the starting materials **1**, the isolated intermediates **3**, and the final products **4** were consistent with their spectral (IR, $^1$H NMR, $^{13}$C NMR) and microanalytical data. The absolute stereochemistry of (*Z*)-**4l** ($R^2$ = *n*-Pr) was unambiguously confirmed by a single crystal X-ray analysis (Figure 1).

The stereocontrol achieved in this McMurry olefination reaction is attributed to a polydentate transient pinacolic intermediate which is formed by homolytic coupling of a radical anion species generated from reduction of the carbonyl compounds **1** ($R^1$ = $SO_2Me$, $R^2$ = H, Me, Et, *n*-Pr, *n*-pentyl, *n*-hexyl, *n*-nonyl) and **2** ($R^3$ = 4-hydroxyphenyl, $R^4$ = Ph) by $Ti^0$.[1] The *Z*-conformer likely arises from a consecutive surface induction of active $Ti^0$ to the polydentate pinacolic intermediate, that is followed by subsequent demetallation and deoxygenation reactions.[4] In this regard, the 'phenoxy-Ti-sulfone' induction plays an important role for *Z*-stereoselection by forcing the sulfonyl and phenoxy moieties to be positioned on the same side (Figure 2). This explanation depicting the stereochemical role of phenoxy and sulfone groups is consistent with the stereochemical outcome observed for a set of control reactions (see Table 1). For example, irrespective of




**Scheme 1** *Reagents and conditions*: (a) Zn, $TiCl_4$, THF, reflux 4.5 h; (b) AcCl, TEA, $Et_2O$, 25 °C, 1.5 h.

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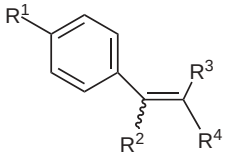
**Table 1** Stereoselective Synthesis of *Z*-Olefins Using a McMurry Reaction




| No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%) | *Z* (%)[a] |
|---|---|---|---|---|---|---|
| **3a** | $SO_2Me$ | H | (4-Br)Ph | Ph | 64 | <56 |
| **3b** | SMe | Me | (4-Me)Ph | Ph | 65 | <65 |
| **3c** | $SO_2Me$ | Me | (4-Me)Ph | Ph | 64 | <66 |
| **3d** | SMe | Et | (4-Me)Ph | Ph | 60 | <60 |
| **3e** | $SO_2Me$ | H | Naphthyl | Ph | 68 | <53 |
| **3f** | $SO_2Me$ | *n*-Pentyl | Naphthyl | Ph | 68 | <61 |
| **3g** | SMe | *n*-Heptyl | Ph | H | 61 | <65 |
| **3h** | SMe | H | (4-OH)Ph | Ph | 63 | <51 |
| **3i** | $SO_2Me$ | Et | (4-OH)Ph | Ph | 75 | >99 |
| **4i** | $SO_2Me$ | Et | (4-OAc)Ph | Ph | 72 | >99 |
| **4j** | $SO_2Me$ | Me | (4-OAc)Ph | Ph | 67 | >90 |
| **4k** | $SO_2Me$ | H | (4-OAc)Ph | Ph | 67 | >90 |
| **4l** | $SO_2Me$ | *n*-Pr | (4-OAc)Ph | Ph | 68 | >99 |
| **4m** | $SO_2Me$ | *n*-Pentyl | (4-OAc)Ph | Ph | 70 | >99 |
| **4n** | $SO_2Me$ | *n*-Hexyl | (4-OAc)Ph | Ph | 70 | >99 |
| **4o** | $SO_2Me$ | *n*-Nonyl | (4-OAc)Ph | Ph | 63 | >99 |

[a] Determined by $^1H$ NMR.

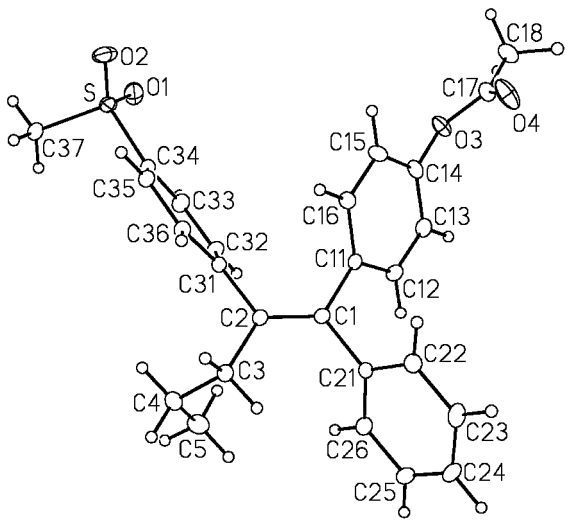



**Figure 1** X-Ray crystal structure of (*Z*)-**4l**.[18]

whether the ketones **1** possessed a $R^1$ $SO_2Me$ or SMe substituent, the cross-coupled reaction with ketones **2** ($R^3$ = 4-bromophenyl, 4-methylphenyl, napthyl or phenyl; $R^4$ = H or Ph) all afforded a mixture of stereoisomers **3** in which the *E*:*Z* ratio was about 2:3 (see products **3a**–**g** in Table 1). A similar reaction of ketone **1** ($R^1$ = SMe; $R^2$ = H) with ketone **2** ($R^3$ = 4-hydroxyphenyl; $R^4$ = Ph) furnished **3h** with a *E*:*Z* ratio of about 1:1. In contrast, the cross-coupled reaction of the ketone **1** ($R^1$ = $SO_2Me$; $R^2$ = Et) with the ketone **2** ($R^3$ = 4-hydroxyphenyl, $R^4$ = phenyl) afforded the *Z*-olefin **3i** exclusively (>99%) since none of the *E*-stereoisomer was detected in the product. These data indicate that a sulfonyl moiety in one carbonyl compound **1** and a hydroxyl moiety in the other carbonyl compound **2** is a requirement for high *Z*-stereoselectivity [see *Z*-products **4i**–**o** that were isolated after acetylation of the corresponding $R^3$ hydroxyphenyl compounds **3**]. Further studies are currently in progress utilizing this stereocontrolled McMurry olefination reaction.

In conclusion, a new methodology has been developed to control the stereochemistry of the McMurry olefination reaction that will have a wide range of synthetic applications.

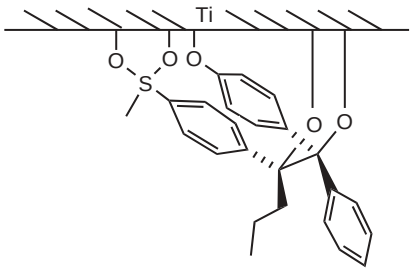



**Figure 2** Proposed mechanism for stereoselective *Z*-olefin formation as illustrated for (*Z*)-1-(4-hydroxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)pent-1-ene: A surface induction pattern involving metallic titanium and the polydentate pinacolic intermediate.[1,4]

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(c) **General Procedure for the Synthesis of Compounds 1. Synthesis of 4-(Methylsulfonyl)butyrophenone (1, $R^1 = SO_2Me$, $R^2 = n$-Pr):** A solution of Oxone® (potassium peroxymonosulfate) (4.06 g, 6.6 mmol) in $H_2O$ (20 mL) was added to a stirred solution of 4-(methylthio)butyrophenone[13] (0.64 g, 3.3 mmol) in 50% THF–MeOH (1:1, v/v; 10 mL) at 0 °C, and the reaction mixture was stirred for 15 h at 25 °C. The solvent was removed in vacuo, $H_2O$ (20 mL) was added to the residue, and the mixture was extracted with EtOAc (3 × 30 mL). The combined EtOAc extracts were washed with $H_2O$, the EtOAc fraction was dried ($Na_2SO_4$), and the solvent was removed in vacuo to afford a white solid which was purified by recrystallization from $CH_2Cl_2$–*n*-hexane (1:9, v/v) to afford **1** ($R^1 = SO_2Me$, $R^2 = n$-Pr) in 89% yield as white needles; mp 86–88 °C. IR (film): 1148, 1313 ($SO_2$), 1698 (C=O) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, 3 H, *J* = 7.3 Hz, C*H*$_3$), 1.73–1.85 (m, 2 H, C*H*$_2$), 2.90 (t, 2 H, *J* = 7.0 Hz, COC*H*$_2$), 3.09 (s, 3 H, $SO_2CH_3$), 8.04 (d, 2 H, *J* = 8.5 Hz, 4-methylsulfonylphenyl H-2, H-6), 8.13 (d, 2 H, *J* = 8.5 Hz, 4-methylsulfonylphenyl H-3, H-5). Anal. Calcd for $C_{11}H_{14}O_3S \cdot 1/6H_2O$: C, 57.61; H, 6.25. Found: C, 57.89; H, 6.25.
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(17) **General Procedure for Synthesis of Compounds 4.** Synthesis of (*Z*)-1-(4-acetoxyphenyl)-1-phenyl-2-(4-methylsulfonylphenyl)pent-1-ene [(***Z***)-**4l**]: $TiCl_4$ (1.83 mL, 13 mmol) was added drop wise to a stirred suspension of Zn powder (1.7 g, 26.5 mmol) in dry THF (30 mL) under argon at –10 °C, and this mixture was refluxed for 2 h. A solution of 4-(methylsulfonyl)butyrophenone (**1**, $R^1 = SO_2Me$, $R^2 = n$-Pr) (0.75 g, 3.3 mmol) and 4-hydroxybenzophenone (**2**, $R^3$ = 4-hydroxyphenyl, $R^4$ = Ph) (0.66 g, 3.3 mmol) in THF (65 mL) was added to the cooled suspension of the titanium reagent at 0 °C, and the reaction mixture was refluxed for 2.5 h. After cooling to 25 °C, the reaction mixture was poured into a 10% aq $K_2CO_3$ solution (100 mL), vigorous stirring was maintained for 5 min, and the dispersed insoluble material was removed by vacuum filtration using Celite 545. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were dried ($Na_2SO_4$), the solvent was removed in vacuo to afford the olefinic intermediate **3** ($R^1 = SO_2Me$, $R^2 = n$-Pr, $R^3$ = 4-hydroxyphenyl, $R^4$ = Ph), which was dissolved in $Et_2O$ (10 mL), and $Et_3N$ (0.5 g, 5.0 mmol) was added. Acetyl chloride (0.39 g, 5.0 mmol) was added drop wise at 0 °C, and the reaction was allowed to proceed for 1.5 h at 25 °C with stirring prior to quenching with $H_2O$ (20 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 30 mL), the combined organic fractions were washed with $H_2O$, and the organic fraction was dried ($Na_2SO_4$). Removal of the solvent in vacuo gave a solid that was purified by flash silica gel column chromatography using *n*-hexaneEtOAc (3:1, v/v) as eluant to afford (***Z***)-**4l** (R = *n*-Pr) as colorless crystals (0.97 g, 68%); mp 132–134 °C. IR (film): 1142, 1322 ($SO_2$), 1585 (C=C), 1757 (C=O of OAc) $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, 3 H, *J* = 7.3 Hz, $CH_2CH_3$), 1.25–1.40 (m, 2 H, $CH_2CH_3$), 2.23 (s, 3 H, OCOC*H*$_3$), 2.44 (t, 2 H, *J* = 7.9 Hz, C=C-C*H*$_2$), 3.04 (s, 3 H, $SO_2CH_3$), 6.76 (d, 2 H, *J* = 8.5 Hz, 4-acetoxyphenyl H-3, H-5), 6.85 (d, 2 H, *J* = 8.5 Hz, 4-acetoxyphenyl H-2, H-6), 7.20–7.40 (m, 7 H, phenyl hydrogens, and 4-methylsulfonylphenyl H-2, H-6), 7.74 (d, 2 H, *J* = 8.5 Hz, 4-methylsulfonylphenyl H-3, H-5). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 14.10 ($CH_2CH_2CH_3$), 17.77 ($CH_3C$=O), 21.16 ($CH_2CH_2CH_3$), 37.64 ($CH_2CH_2CH_3$), 44.53 ($SO_2CH_3$), 120.69, 126.99, 127.11, 128.26, 129.23, 130.44, 131.46 ($C_{arom}$-H), 138.03, 139.44, 139.53, 140.53, 142.22, 148.64, 148.96 ($C_{arom}$-C, $C_{olefin}$-C, $C_{arom}$-O, $C_{arom}$-S), 169.00 ($CH_3C$=O). Anal. Calcd for $C_{26}H_{26}O_4S$: C, 71.86; H, 6.03; S, 7.38. Found: C, 71.74; H, 5.96; S, 7.27.

(18) Crystal data for (*Z*)-**4l**: Molecular formula: $C_{26}H_{26}O_4S$, formula weight: 434.53, crystal system: monoclinic, space group: $P2_1/c(14)$ with unit cell dimensions $a$ = 8.0403 (6) Å, $b$ = 14.5485 (12) Å, $c$ = 19.9285 (16) Å, $\beta$ = 101.4182 (15)º, $V$ = 2285.0 (3) Å$^3$, $Z$ = 4, = 1.263 gcm$^{-3}$, $\mu$ = 0.171 mm$^{-1}$. A crystal fragment of approximate dimensions(mm$^3$) 0.73 × 0.40 × 0.04 was mounted in a nonspecific orientation on Bruker PLATFORM/SMART 1000 CCD diffractometer. All intensity measurements were performed using Mo K$\alpha$ radiation ($\lambda$ = 0.71073 Å) with a graphite crystal incident beam monochromator. The intensity data were collected at –80 °C using an $\omega$ scan (0.3º) (10 s exposures). A total 4675 independent reflections were collected to a maximum 2$c$ limit at 52.9°. The structure was solved by direct methods. Refinement of atomic parameters was carried out by using full-matrix least-squares on F$^2$ (SHELXL-93), giving final agreement factor (R indices) of $R1$ = 0.0484 and $wR2$ = 0.1116. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 228635. Copies of the data can be obtained free of charge by application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk).