

Origins of Aryl Substituent Effects on the Stereoselectivities of Additions of Silyl Enol Ethers to a Chiral Oxazolinium Ion

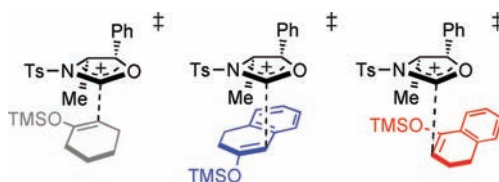
Elizabeth H. Krenske*

School of Chemistry, University of Melbourne, Victoria 3010, Australia, and Australian Research Council Centre of Excellence for Free Radical Chemistry and Biotechnology

ekrenske@unimelb.edu.au

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ABSTRACT



Density functional theory calculations are reported that reveal the role of aromatic interactions in the additions of aryl-substituted silyl enol ethers to a chiral oxazolinium ion. Aryl-substituted silyl enol ethers give the opposite diastereomer of the adduct than do aliphatic silyl enol ethers, due to a combination of attractive cation– π and CH– π interactions, reduced steric repulsion, and lower torsional strain in the more “crowded” transition state.

There is growing interest among synthetic chemists in the use of aromatic groups as stereodirecting elements.¹ Herein, theoretical calculations are used to provide the first explanation for unexpected aryl-substituent effects observed in an asymmetric formylation reaction. The reaction, reported by Hoppe,² involves the Lewis acid-catalyzed addition of the chiral 2-methoxy-3-sulfonyl-1,3-oxazolidine **1** to a silyl enol ether (Scheme 1), and is representative of a formylation strategy that was pioneered by both Hoppe^{2,3} and Scolastico.⁴ The Lewis acid-catalyzed reactions of **1** with silyl enol ethers **2a–c** afford the diastereomeric, masked α -formyl ketones **3** and **4**, with selectivities reaching > 95:5. Unexpectedly, however,

opposite stereoselectivities were obtained depending on whether an aliphatic or an aryl-substituted silyl enol ether was used.² Cyclohexenol TMS ether **2a** gave predominantly the *2R*-adduct (**3**), but the aryl-substituted analogues **2b** and **2c** gave predominantly *2S*-adducts (**4**).⁵ Prompted by the increasing ability of theory to uncover new forms of aryl-induced stereocontrol, a density functional theory investigation of the aryl effect on Hoppe's asymmetric formylation is reported here.

The Lewis acid-catalyzed reactions of the oxazolidine **1** with silyl enol ethers are believed to proceed via intermediate oxazolinium cations of the type **5**.⁶ Hoppe proposed that the transition states giving rise to diastereomers **3** and **4** adopt the conformations **TS-3** and **TS-4**, respectively (Scheme 2). The antiperiplanar arrangement of the C=C and C=O bonds was suggested on the basis of Noyori's work⁷ on additions of silyl enol ethers to oxonium cations, where the *anti* conformation was proposed to

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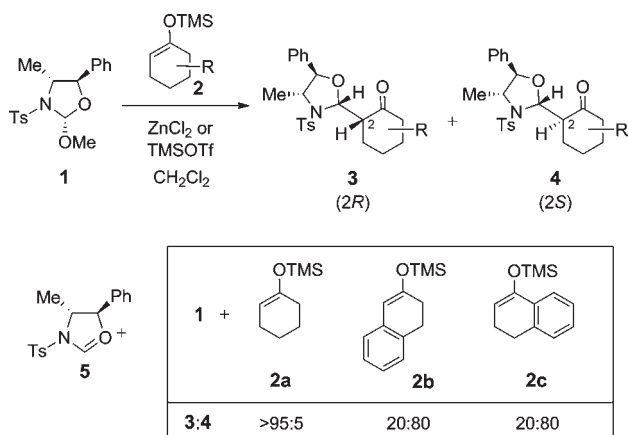
(4) (a) Bernardi, A.; Cardani, S.; Carugo, O.; Colombo, L.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 2779–2782. (b) Palazzi, C.; Poli, G.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4223–4226. (c) Bernardi, A.; Cavicchioli, M.; Poli, G.; Scolastico, C.; Sidjimov, A. *Tetrahedron* **1991**, *47*, 7925–7936.

(5) A similar reversal of stereoselectivity, with drs reaching > 95:5, was observed with aliphatic and aryl-substituted cyclopentenol TMS ethers (ref 2).

(6) (a) Tomalia, D. A.; Paige, J. N. *J. Org. Chem.* **1973**, *38*, 422–430. (b) Bernardi, A.; Cardani, S.; Poli, G.; Potenza, D.; Scolastico, C. *Tetrahedron* **1992**, *48*, 1343–1352.

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Scheme 1. Hoppe's Asymmetric Additions of Silyl Enol Ethers to a Chiral 2-Methoxy-3-sulfonyl-oxazolidine²

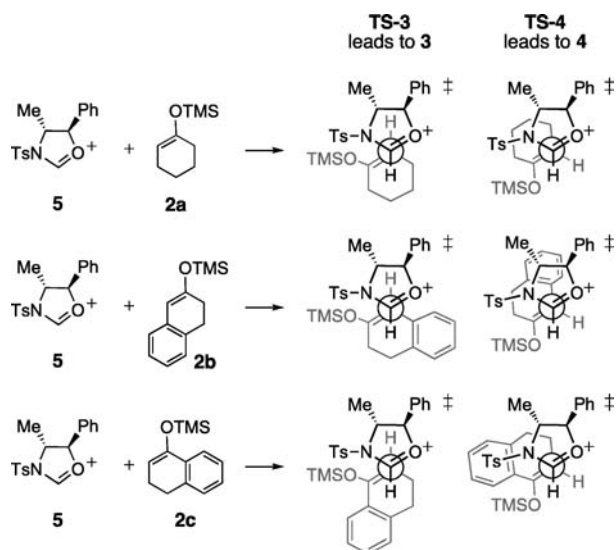


minimize electrostatic repulsion between the oxonium oxygen and the developing positive charge on the silyl enol ether. On this basis, the selectivity for **4** displayed by silyl enol ethers **2b** and **2c** is surprising, as **TS-4** appears much more sterically crowded than **TS-3**. Hoppe tentatively suggested that **TS-4** may be stabilized by an attractive interaction between the tosyl group and the aromatic ring.

The factors controlling stereoselectivity in the reactions of **5** with silyl enol ethers were studied here by means of density functional theory calculations in Gaussian 09.⁸ Geometry optimizations and conformational searching were performed at the B3LYP/6-31G(d) level.⁹ Energies were calculated both with B3LYP and with three newer functionals that include corrections for dispersion (B3LYP-D,¹⁰ B97-D,^{10,11} and M06-2X¹²). This type of approach has previously been used to study aryl effects on stereoselectivities of cycloaddition reactions¹³ and has more generally been shown to be superior to B3LYP alone for polar reactions of large molecules.¹⁴

The geometry of the oxazolinium cation **5** is shown in Figure 1. Although **5** is often drawn with a C=O double bond, the alternative iminium representation is actually of slightly greater importance. The CN and CO bond lengths in **5** (1.31 and 1.29 Å, respectively) are both within 0.03 Å of true double bond values, as judged from the model iminium and oxonium cations **6** and **7**. The HOMO and

Scheme 2. Transition State Geometries Proposed² for Additions of Silyl Enol Ethers **2a–c** to the Oxazolinium Ion **5**



LUMO of the oxazolinium ring have almost equal coefficients on N and O, with a slightly greater contribution from nitrogen.¹⁵

When **5** is drawn in its iminium form, the proposed *anti*-C=C...CO transition state geometries can be seen to conform to Seebach's topological rule for additions of π -systems,¹⁶ insofar as the donor C=C π -bond is gauche to both the acceptor C=N π -bond and the smallest substituent (H) on the acceptor.

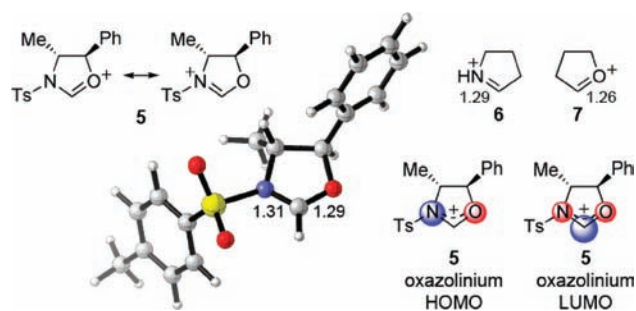


Figure 1. Calculated geometry of the oxazolinium cation **5** and related bond lengths in model compounds (B3LYP/6-31G(d) geometries, distances in Å).

Transition states were computed for the reaction of **5** with the aliphatic silyl enol ether **2a**. The two lowest-energy TS conformers (**TS-3a** and **TS-4a**) are shown in Figure 2. Both possess the proposed antiperiplanar C=C...CO geometry. All four density functional methods correctly

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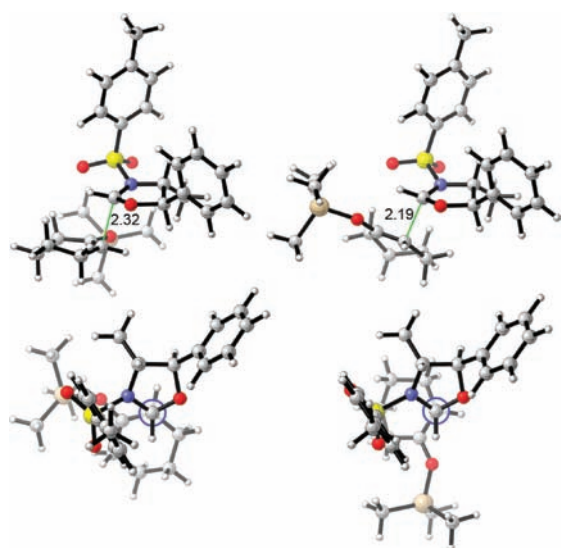
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(15) Orbital coefficients ($2p_y$ contributions) calculated at the HF/6-31G//B3LYP/6-31G(d) level: HOMO, N –0.23, O 0.19; LUMO, N 0.16, O 0.16.

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$\Delta H_{\text{rel}}^{\ddagger}$		TS-3a	TS-4a
B3LYP	0	1.9	2.6
B3LYP-D	0	2.6	2.9
B97-D	0	2.9	2.2 (2.2)
M06-2X	0 (0)	2.2 (2.2)	

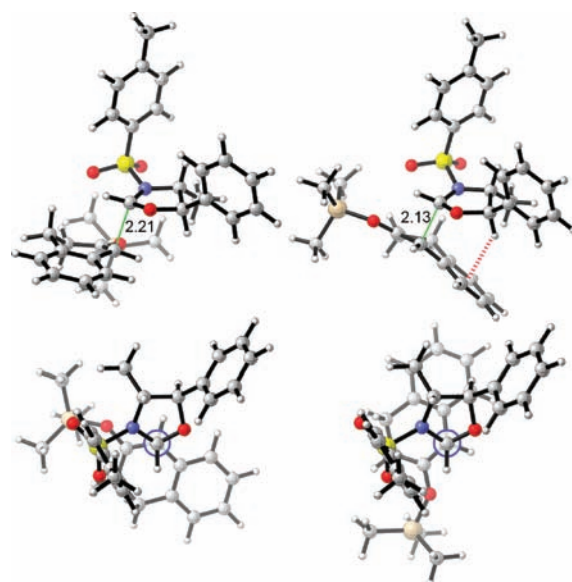
Figure 2. Diastereomeric transition states for reaction of oxazolinium cation **5** with the silyl enol ether **2a** (B3LYP/6-31G(d) geometries). The bottom view shows the Newman projection down the forming C–C bond. Values of $\Delta H_{\text{rel}}^{\ddagger}$ (kcal/mol) were obtained using the 6-31G(d) basis set, except for the values in parentheses, which employ the 6-311+G(d,p) basis. Distances are in Å.

predict **3a** to be the favored product.¹⁷ The computed stereoselectivity, based on the two pictured conformers alone, is $\Delta\Delta H^{\ddagger} = 1.9\text{--}2.9$ kcal/mol ($\Delta\Delta G^{\ddagger} = 1.8\text{--}2.7$ kcal/mol).

The stereoselectivity for **2a** is primarily related to torsional strain about the forming C–C bond. Steric clashing in the more “crowded” transition state **TS-4a** is actually no more severe than in **TS-3a**, but the avoidance of steric clashing in **TS-4a** is achieved only at a cost of rotating the forming C–C bond into a partially eclipsed arrangement. The Newman projections at the bottom of the Figure show the small dihedral angles in **TS-4a** (31–36°). In contrast, the favored transition state (**TS-3a**) is quite well staggered (50–51°).

Transition states for the corresponding reaction with the aryl-fused silyl enol ether **2b** are shown in Figure 3. Here, the transition states again adopt antiperiplanar C=C⋯CO arrangements, but the partial eclipsing that was present in **TS-4a** is not found in **TS-4b**. The stereoselectivity instead originates from interactions between **5** and the aromatic ring of **2b**. Whereas **TS-4a** contained a close steric contact involving the CH₂ group adjacent to the forming bond, in **TS-4b** this is replaced by a weak attractive interaction between the aromatic π -cloud and the positively charged atoms of the oxazolinium ring. The H-5 proton of the oxazolinium ion lies closest to the π -cloud of the aromatic ring (hashed line).

Only the three density functionals that include terms to represent dispersion correctly predict **TS-4b** to be favored



$\Delta H_{\text{rel}}^{\ddagger}$		TS-3b	TS-4b
B3LYP	0	0	0.6
B3LYP-D	0	0	-0.6
B97-D	0	0	-0.3
M06-2X	0 (0)	0 (0)	-0.3 (-0.8)

Figure 3. Diastereomeric transition states for reaction of oxazolinium cation **5** with the silyl enol ether **2b**. Basis sets are as described in Figure 2.

over **TS-3b**. This is in keeping with the underlying role of dispersion in CH– π interactions in general.^{1,18} The dispersion-inclusive methods predict **TS-4b** to be favored by 0.3–0.6 kcal/mol. B3LYP, which lacks dispersion corrections, favors **TS-3b** by 0.6 kcal/mol.

Transition states for the reaction of **5** with silyl enol ether **2c** are shown in Figure 4. Here, both aromatic interactions and torsional differences control the stereoselectivity. **TS-3c** adheres to the *anti* C=C⋯CO geometry, but **TS-4c** adopts a gauche arrangement with the C=C bond lying underneath the oxazolinium ring. The gauche conformation avoids destabilizing steric clashes and allows for a weakly stabilizing interaction between the aromatic π -system and the oxazolinium ring. Proton H-5 in **TS-4c** lies closest to the aromatic π -cloud, albeit with a longer H⋯C_{arom} separation than in **TS-4b** (2.92 and 2.71 Å, respectively). **TS-4c** is further stabilized by torsional strain differences; its forming bond is well staggered (dihedrals 55–60°) whereas **TS-3c** is partially eclipsed (37–43°).

All four functionals correctly predict **TS-4c** to be favored, but B3LYP underestimates the selectivity compared to the other three functionals. The stereoselectivity based on the two pictured TS conformations is 1.8–3.9 kcal/mol.

(17) Additions of **2a–c** to **5** were found to be exothermic by at least 28 kcal/mol (M06–2X), and likely to be under kinetic control under the reaction conditions (0 °C, CH₂Cl₂).

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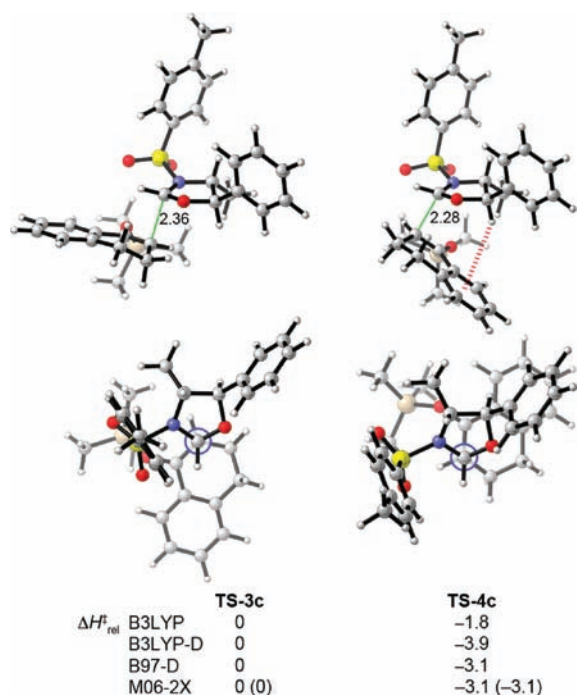


Figure 4. Diastereomeric transition states for reaction of oxazolinium cation **5** with the silyl enol ether **2c** (B3LYP/6-31G(d) geometries). Basis sets are as described in Figure 2.

To estimate the degree to which aromatic interactions contribute to the overall transition-state stabilization for **2b/c**, the aromatic ring [(CH)₄ fragment] was deleted, and the two free valences were filled with H atoms.¹⁹ Removal of the aromatic ring from **2b** completely reversed the selectivity, such that **TS-3** was favored by 1.0 kcal/mol ($\Delta\Delta E^\ddagger$, B3LYP-D). For **2c**, the selectivity for **TS-4** persisted, but was 0.5 kcal/mol smaller. The aromatic interactions are the primary influence on stereoselectivity for **2b**, while for **2c** they act in concert with the torsional strain effects.

(19) H atoms were appended at a distance of 1.09 Å, with the same bond angles and dihedrals as the original carbon atoms. All other remaining geometrical parameters were left unchanged.

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Table 1. Computed Stereoselectivities in the Gas Phase and in Dichloromethane for Additions of **2a–c** to the Oxazolinium Ion **5**^a

reactant	$\Delta\Delta G^\ddagger$ (gas phase)	$\Delta\Delta G^\ddagger$ (CH ₂ Cl ₂)
2a	2.0	3.4
2b	0.0	0.7
2c	-2.0	-0.3

^a $\Delta\Delta G^\ddagger(\text{TS-4}-\text{TS-3})$, M06-2X/6-311+G(d,p)//B3LYP/6-31G(d), kcal/mol. Solution values incorporate CPCM solvation energies computed at the M06-2X/6-31G(d) level.

The stabilization provided by the cation- π and CH- π interactions in **TS-4b/c** is expected to be sensitive to solvation. Solvation energies in dichloromethane were computed with the CPCM method,²⁰ and the results are shown in Table 1. The computed $\Delta\Delta G^\ddagger$ values capture the solution-phase stereoselectivity for **2c** but not for **2b** (a full treatment would require consideration of other low-lying TS conformers). They do, however, reflect the expected attenuation of aromatic interactions in solution.

In summary, DFT calculations provide a clear explanation for the unexpected aryl-substituent effects on stereoselectivity in Hoppe's asymmetric formylation reaction. The aryl substituent controls stereoselectivity by alleviating torsional strain, and by replacing repulsive steric interactions with attractive aromatic interactions. These stereocontrol elements are likely to be relevant to various other asymmetric reactions. Theory continues to reveal an increasing repertoire of aryl-substituent effects on stereoselectivity.

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Supporting Information Available. Calculated geometries and energies, and a complete citation for ref 8. This material is available free of charge via the Internet at <http://pubs.acs.org>.