SHORT COMMUNICATION

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# On the Origin of *E*/*Z* Selectivity in the Modified Julia Olefination – Importance of the Elimination Step

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*Dedicated to Professor Alois Fürstner on the occasion of his 50th birthday*

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The mechanism and origin of high *E* selectivity in the modified Julia olefination of aromatic aldehydes have been explored by computational and experimental means. Reversibility of addition and hence selectivity of the formation of sulfinate **5** is very variable and depends on the nature of the sulfone substrate. However, in all cases, elimination occurs through a concerted antiperiplanar and synperiplanar mechanism for sulfinates *anti*-**5** and *syn*-**5**, respectively. Both *syn* and *anti* diastereomeric pathways thus lead preferentially to the (*E*)-alkene.

## Introduction

The modified Julia olefination allows the synthesis of alkenes in a single step from metallated benzothiazol-2-yl (BT) sulfones and aldehydes (Figure 1).[1,2] Over the past two decades, this olefination reaction has emerged as a powerful tool for carbon–carbon double bond formation, in particular when two complex molecular fragments should be connected.[3] The attractiveness of this connective olefination reaction arises from its versatility, its wide functional group tolerance, and the mild reaction conditions under which the reaction proceeds. The only shortcoming of the reaction is the difficulty of predicting and controlling the stereoselectivity of the newly formed double bond, which is a limitation to an even broader use of this reaction.

The experimental results showed that the stereochemical outcome of this process depends highly on the nature of the reactants: reaction of BT-sulfones **2** with aromatic aldehydes (compound **1**, $R^2$ = aryl) generally gives high *E* selectivity, whereas their reaction with aliphatic aldehydes (compound **1**, $R^2$ = alkyl) furnishes alkenes with little or no stereochemical bias.[1,4]

Although the global mechanistic sequence depicted in Figure 1 is known and widely accepted since the pioneering work of S. Julia, a detailed atomistic account of the mechanism and selectivity of this reaction is still lacking.[5]

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In the reaction of lithiated alkyl-BT-sulfones with alkyl aldehydes ($R^1$, $R^2$ = alkyl), S. Julia et al. showed that the initial addition is nonreversible and that subsequent steps are stereospecific, elimination occurring exclusively by a concerted antiperiplanar elimination (i.e. from *transoid* **5**).[5] The low selectivity observed in these cases is thus a direct consequence of the poor diastereocontrol in the initial addition step of sulfone anion **2** onto aldehyde **1**.

For aromatic aldehydes ($R^2$ = Ar), the situation is different: elimination from **3** is not stereospecific.[5,6] In order to account for this nonstereospecificity of the elimination and the observed high *E* selectivity, Julia et al. suggested that in these cases elimination occurs by a direct loss of benzothiazolonate from intermediates **5** to yield a zwitterion such as **6**.[5c] Stabilization of **6** by the aryl group should allow conformational equilibration and favor formation of the (*E*)-olefin upon loss of $SO_2$ from the more stable *anti* zwitterion **6**.

## Results and Discussion

In our calculations[7–9] on the reaction of benzaldehyde with lithiated ethyl- and benzyl-BT-sulfones (**2a** and **2b**), we find a slightly exothermic addition step to form alkoxides **3** (Figure 2). For the *syn* alkoxide (*syn*-**3**), the free energy barrier to Smiles rearrangement[10,11] is computed to be lower than that for addition, thus predicting a nonreversible addition in both cases ($R^1$ = Me or Ph).[12] In the case of the *anti* isomer, unfavorable 1,2 steric interactions in **TS-Smiles** (Smiles transition state) lead to an increase of the barrier to Smiles rearrangement.[13] This has the result that addition of benzyl-BT-sulfone **2b** ($R^1$ = Ph) becomes reversible. These predictions could be confirmed by crossover ex-

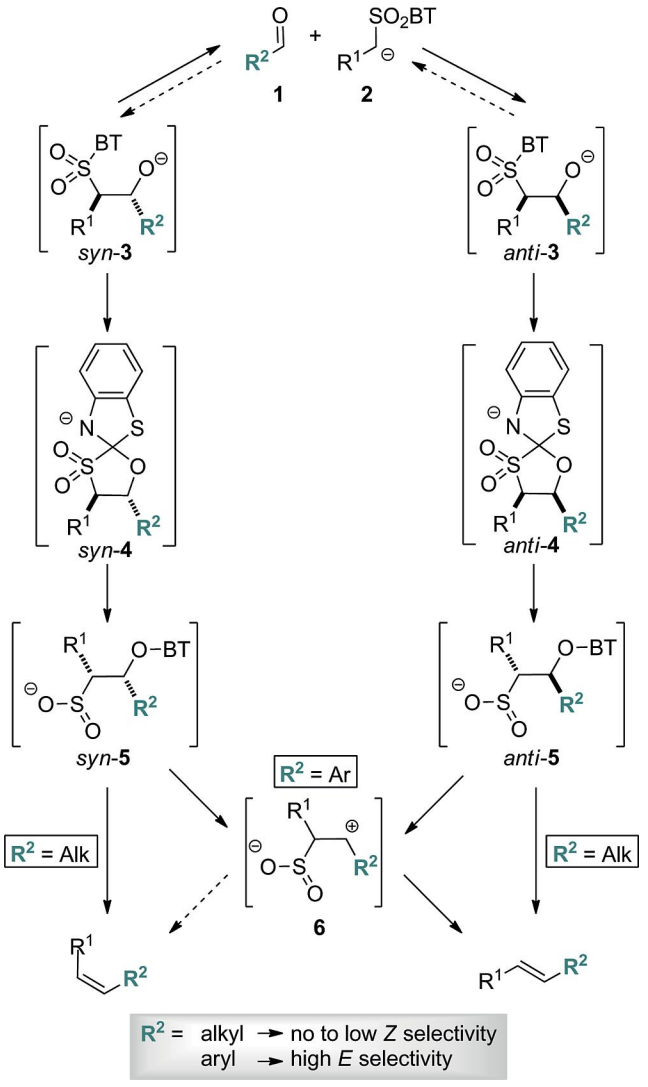



Figure 1. Generally accepted mechanism and selectivity in the modified Julia reaction.

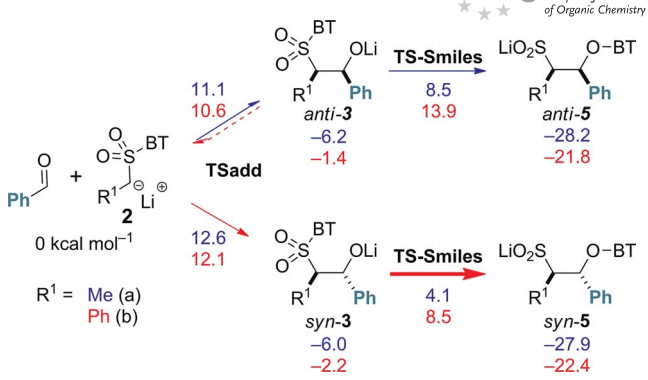
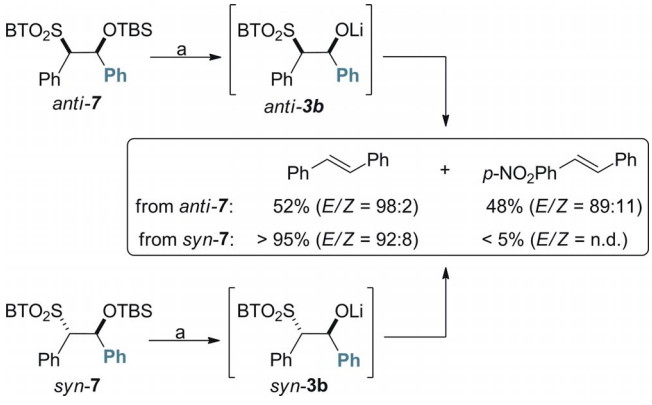



Figure 2. Computed pathways for the formation of sulfinate **5** (free energies in kcal mol$^{-1}$ relative to reactants).




Scheme 1. Crossover experiments. Reagents and conditions: (a) TBAF (2 equiv.), LiCl (5 equiv.), *p*-$NO_2C_6H_4CHO$ (1.1 equiv.), THF, –78 °C.

periments in which the two diastereomeric β-alkoxy-BT-sulfones **3b** ($R^1$ = $R^2$ = Ph) were independently generated by another route in the presence of a more reactive aldehyde (Scheme 1).[6] Indeed, deprotection of *anti*-**7** and *syn*-**7** in the presence of *p*-$NO_2C_6H_4CHO$ gave 48% and <5% of the olefin, respectively, in which the more reactive aldehyde had been incorporated, proving the (at least partial) reversibility of the alkoxide formation in the former case and the nonreversible character of the *syn* addition.

As a consequence, sulfinate adducts **5** should be formed with a low *anti* selectivity in the case of ethyl-BT-sulfone (**2a**), addition being nonreversible and poorly selective.[6] On the other hand, for benzyl-BT-sulfone (**2b**) the observed reversibility of *anti* addition should yield predominantly *syn* sulfinate **5**.[14]

Accordingly, if the elimination step were stereospecific via an antiperiplanar arrangement as in the reaction of aliphatic aldehydes,[1,5] our calculations would predict an *E* selectivity for the reaction of ethyl-BT-sulfone (**2a**) and a preference for (*Z*)-alkene formation for the reaction of benzyl-BT-sulfone (**2b**). Experimentally, a high *E* selectivity (> 96:4) is observed in both cases.[1] Indeed, as postulated by Julia and shown by our crossover experiments (see *E*/*Z* selectivity for stylbene formation in Scheme 1),[6] both diastereomeric pathways lead, in fact, to (*E*)-alkene.

In order to identify the mechanism of formation of (*E*)-alkene from sulfinate **5**, we thus investigated the formation of zwitterion **6** as proposed by Julia et al.[5c] Every attempt to optimize such an intermediate, or a carbanion resulting from the loss of $SO_2$, failed, our results favoring a concerted elimination instead.[15]

However, while our calculations indicate that *anti* isomers should undergo antiperiplanar elimination to give (*E*)-olefins, *syn* isomers are actually predicted to preferentially eliminate from *cisoid syn*-**5** by a concerted synperiplanar elimination, thus leading also to (*E*)-alkenes (Figures 3 and 4).[12]

In order to provide experimental evidence for this concerted elimination from *cisoid syn*-**5** (synperiplanar elimination) in the reaction of aromatic aldehydes, we performed deuterium-labeled experiments. We reasoned that if we could form stereoselectively monodeuterated **5**-***d***, in which 1,2 steric strain is absent, we would get information on the

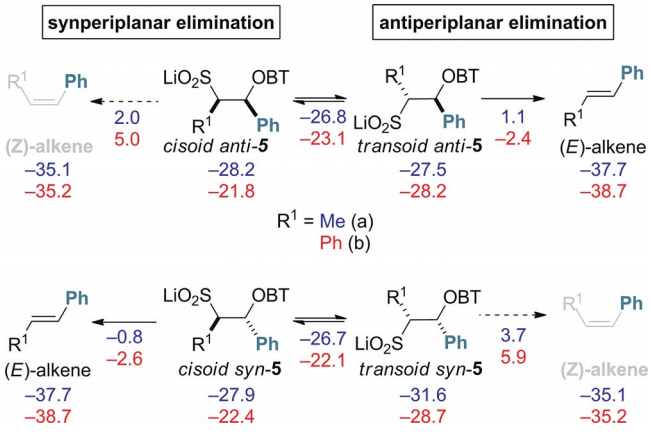



Figure 3. Computed pathways for alkene formation from **5** (free energies in kcal mol$^{-1}$ relative to reactants).

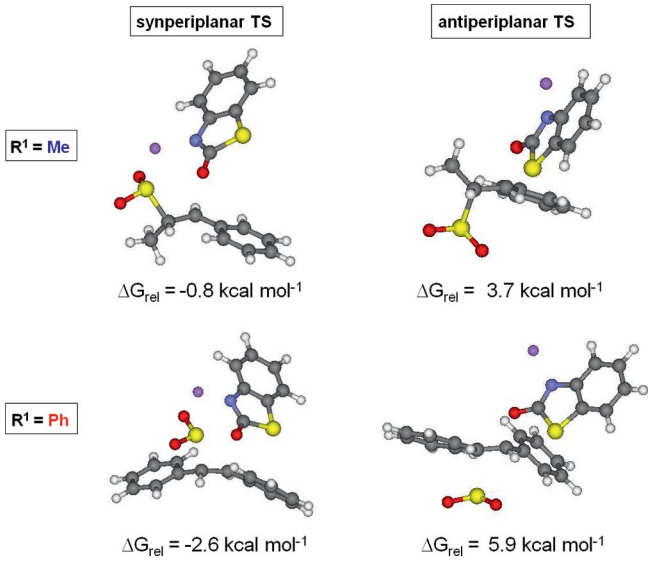


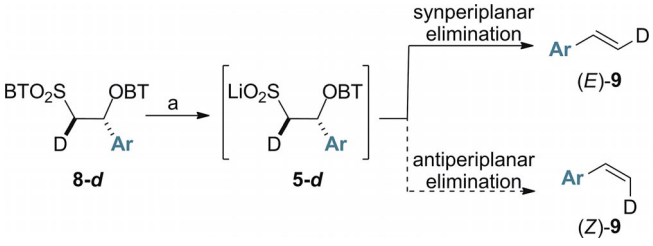

Figure 4. Transition state structures for the elimination step from *syn*-**5a** (top) and *syn*-**5b** (bottom) (free energies in kcal mol$^{-1}$ relative to reactants).

mechanism of the elimination (Table 1). Indeed, if elimination from **5-*d*** involves formation of a carbocation such as **6**, an approximately 50:50 mixture of (*E*)- and (*Z*)-styrene-(β)-*d* would be obtained, whereas if elimination occurs selectively by a concerted mechanism, only one isomer would be formed: the (*E*)-alkene if elimination is synperiplanar and the (*Z*)-alkene if it is antiperiplanar. Addition of EtSLi onto **8-*d*** [6,16] at –78 °C allowed clean formation of sulfinates **5-*d***, which immediately undergo elimination to provide the corresponding deuterated styrenes.[17] In each case, selective (*E*)-alkene formation was observed. These results thus give support to the concerted synperiplanar elimination mechanism.

Analysis of elimination TSs for the reaction of **2a** and **2b** shows that an important factor contributing to this unexpected preference for synperiplanar elimination from *syn*-**5** is the destabilizing 1,2 steric strain present in the antiperiplanar TS (but absent in the synperiplanar one). This interaction also explains the fact that, in the case of *anti*-**5** isomer, it is the antiperiplanar elimination which is favored (see Figure 3). Indeed, in this case it is the synperiplanar TS which involves this unfavorable 1,2 steric interaction. Another difference between the two transition state structures is the degree of coordination to the lithium cation: the synperiplanar TS involves coordination of lithium by both the sulfinate and the BT groups, whereas the antiperiplanar arrangement allows coordination only by the BT group (see Figure 4).[18]

This leaves, however, the question of why *syn*-**5** undergoes synperiplanar elimination in the reaction of aromatic aldehydes while exclusive antiperiplanar elimination is observed in the reaction of alkyl aldehydes.[5] Calculations on model systems reveal that the presence of the phenyl group also plays an important role in the electronic stabilization of the synperiplanar TS: Substitution by a phenyl group leads to a higher stabilization (by 2.8 kcal mol$^{-1}$) of the synperiplanar TS than the antiperiplanar one (Table 2). A natural bond orbital (NBO) analysis shows that the key interaction responsible for this activation is an electronic donation from the π system of the phenyl to the positively charged aldehyde carbon atom of the TS. Corresponding *E*(2) values are 58.4 and 52.8 kcal mol$^{-1}$ for syn- and antiperiplanar TSs, respectively,

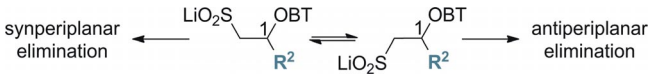
Table 1. Deuteration experiments.[a]




| Entry | Ar | Olefin | Yield [%][b] | *E*/*Z*[c,d] |
|---|---|---|---|---|
| 1 | *p*-ClC$_6$H$_4$ | **9a** | 89 | 81:19 |
| 2 | C$_6$H$_5$ | **9b** | 92 | 90:10 |
| 3 | *p*-MeOC$_4$H$_6$ | **9c** | 87 | 94:6 |

[a] Reaction conditions: EtSH (1.2 equiv.), LiHMDS (1.1 equiv.) THF, –78 °C (2 h) to room temp. (6 h). [b] Refers to the pure isolated compound. [c] Based on the crude $^1$H NMR spectra. [d] Mean of three independent experiments.

Table 2. Influence of the nature of the aldehyde (R$^2$) on the stereoselectivity of the elimination (free activation energies in kcal mol$^{-1}$ from *transoid* sulfinates).




| | TS synperiplanar | | | TS antiperiplanar | | |
|---|---|---|---|---|---|---|
| R$^2$ | Δ$G_{rel}$ | $d_{C-O}$[a] | Charge on C(1)[b] | Δ$G_{rel}$ | $s_{C-O}$[a] | Charge on C(1)[b] |
| H | 30.5 | 2.07 | 0.329 | 30.9 | 2.00 | 0.241 |
| Me | 32.1 | 2.16 | 0.347 | 33.8 | 2.00 | 0.302 |
| Ph | 25.9 | 1.98 | 0.354 | 29.1 | 1.96 | 0.323 |

[a] C(1)–O distances (in Å) in the TS. [b] NPA (natural population analysis) charges (in a. u.) in TS.

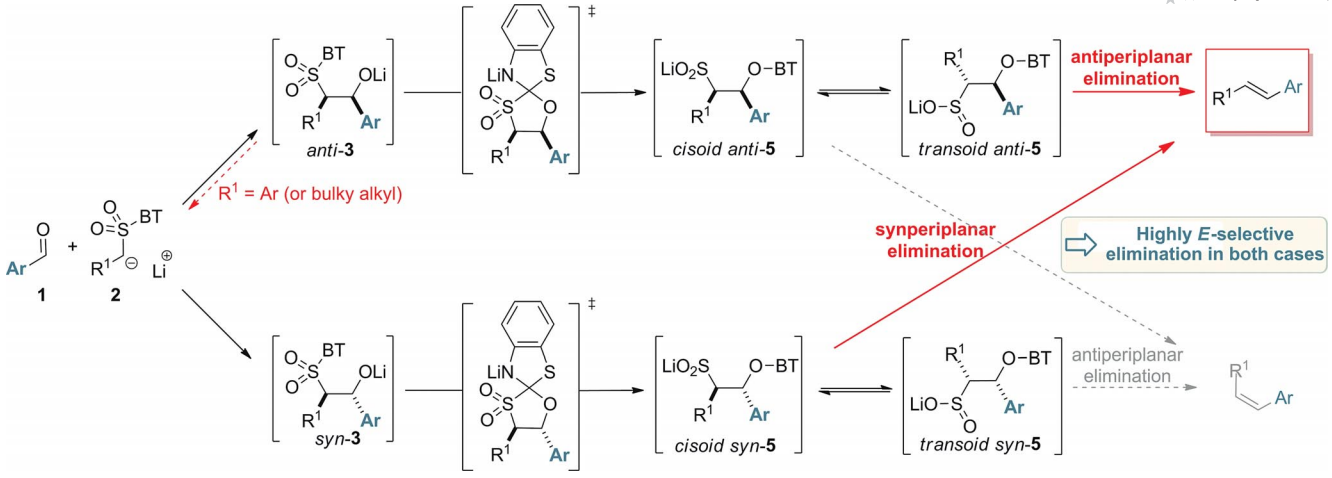



Figure 5. Rationale for observed high *E* selectivity in modified Julia olefination of aromatic aldehydes.

consistent with a higher stabilization in the former case, probably because of the slightly more positively charged C(1) carbon atom in the synperiplanar TSs (see Table 2).

Interestingly, the higher stabilization of the synperiplanar TS by electronic donation from the aryl group suggests an explanation for the fact that electron-poor aldehydes give lower *E* selectivities than electron-rich ones:[5c] Electron-poor aryl groups stabilize elimination TSs to a lesser extent, thus decreasing the preference for synperiplanar elimination, and hence they lower the *E*/*Z* selectivity. This is supported by the decrease of the *E*/*Z* ratio upon going from *p*-methoxy- to *p*-chloro-substituted aryl derivatives in our crossover experiments (see Table 1).

## Conclusions

In summary, we have clarified the mechanism of elimination in modified Julia reactions of aromatic aldehydes and showed that elimination occurs through a concerted antiperiplanar and synperiplanar mechanism in the case of *anti*- and *syn*-sulfinate, respectively. The high experimental *E* selectivity is thus explained by *E*-selective elimination, from both the *syn* and the *anti* diastereomer (Figure 5). Identification of synperiplanar elimination as the main pathway for elimination from *syn*-sulfinate and understanding of factors controlling the stereoselectivity of elimination now allow us to rationalize some key experimental observations relating to modified Julia olefination of aromatic aldehydes and lithiated BT-sulfones. This analysis should assist in the design of new reagents and reaction conditions and allow further development of the modified Julia reaction process for highly *E*/*Z*-selective synthesis of alkenes.

**Supporting Information** (see footnote on the first page of this article): Full computational and experimental details including procedures and characterization data for all compounds and optimized Cartesian coordinates of all optimized structures.

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[1] For reviews, see: a) I. E. Markó, J. Pospíšil in *Science of Synthesis*, vol. 47b (Ed.: A. de Meijere), Thieme, Stuttgart, New York, **2010**, pp. 105–160; b) C. Aïssa, *Eur. J. Org. Chem.* **2009**, 1831–1844; c) K. Plesniak, A. Zarecki, J. Wicha, *Top. Curr. Chem.* **2007**, *275*, 163–250; d) R. Dumeunier, I. E. Markó in *Modern Carbonyl Olefination* (Ed.: T. Takeda), Wiley-VCH, Weinheim, **2004**, pp. 104–150; e) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.

[2] Several heteroaryl substrates have been developed for this process and the nature of the heteroaryl group has shown to have, in some cases, an influence on the *E*/*Z* selectivity (see ref.[1]). BT-sulfones being the original, and still most popular, substrates in modified Julia reaction, the present study will focus on such systems.

[3] The modified Julia olefination is commonly used in total syntheses of natural and unnatural biologically active molecules. For selected examples, see ref.[1d] and a) R. Cribiú, C. Jäger, C. Nevado, *Angew. Chem.* **2009**, *121*, 8938–8941; *Angew. Chem. Int. Ed.* **2009**, *48*, 8780–8783; b) K. Sastraruji, T. Sastraruji, S. G. Pyne, A. T. Ung, A. Jatisatienr, W. Lie, *J. Nat. Prod.* **2010**, *73*, 935–941; c) K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064–14066; d) J. Santos, B. M. Illescas, N. Martín, J. Adrio, J. C. Carretero, R. Viruela, E. Ortí, F. Spänig, D. M. Guldi, *Chem. Eur. J.* **2011**, *17*, 2957–2964; e) C. Rink, F. Sasse, A. Zubriene, D. Matulis, M. E. Maier, *Chem. Eur. J.* **2010**, *16*, 14469–14478; f) P. Gowrisankar, S. A. Pujari, K. P. Kaliappan, *Chem. Eur. J.* **2010**, *16*, 5858–5862.

[4] Despite numerous experimental studies, no general solution to the control of this *E*/*Z* selectivity could be found thus far. See: a) F. Billard, R. Robiette, J. Pospíšil, *J. Org. Chem.* **2012**, *77*, 6358–6364; b) J. Pospíšil, *Tetrahedron Lett.* **2011**, *52*, 2348–2352; c) S. Surprenant, W. Y. Chan, C. Berthelette, *Org. Lett.* **2003**, *5*, 4851–4854; d) P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26–28; e) A. B. Charette, H. Lebel, *J. Am. Chem. Soc.* **1996**, *118*, 10327–10328.

[5] a) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175–1178; b) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357; c) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878.

[6] See Supporting Information for full details and complementary experiments.

  

[7] Calculations were carried out at the SCS-MP2/aug-cc-pVTZ(THF)//B3LYP/6–31+G*(THF) level of theory with the Jaguar 6.5[8] and ORCA 2.7[9] programs. Unless mentioned otherwise, reported energies are free energies relative to reactants. Since the nature of the counterion has a small influence on the *E*/*Z* selectivity (see ref.[4]), a lithium cation was included in all our calculations, LDA being the most common base used in these reactions. See Supporting Information for full computational details.

[8] *Jaguar*, version 6.5, Schrödinger, LLC, New York, NY, **2005**.

[9] F. Neese, ORCA, *An Ab Initio, DFT, and Semiempirical Electronic Structure Package*, version, 2.7.0, University of Bonn, Germany, **2010**.

[10] Interestingly, our results indicate that, conversely to what is commonly admitted, transfer of the heterocycle occurs by a concerted pathway, i.e., in a single elementary step (see the Supporting Information for full details). For a study on single-step and multistep mechanisms of aromatic nucleophilic substitution, see: M. N. Glukhovstev, R. D. Bach, S. Laiter, *J. Org. Chem.* **1997**, *62*, 4036–4046.

[11] For a review on Smiles rearrangement, see W. E. Truce, E. M. Kreiber, W. W. Brand in *Organic Reactions*, vol. 18, John Wiley & Sons, New York, **1970**, p. 99.

[12] The barrier to rotation (between *cisoid* and *transoid* conformers) in alkoxides and sulfinates indicates, in both cases, a rapid equilibrium that has no important role in determining reactivity or selectivity. See the Supporting Information for full data.

[13] This is in good agreement with experiments, which showed a higher stability of *anti*-β-alkoxy-BT-sulfones over their *syn* isomers (see ref.[5b]).

[14] One may expect sterically hindered alkyl-BT-sulfones to involve increased barriers to Smiles rearrangement for *anti* isomers, which in turn could lead to a reversal of addition. In these cases, a *syn* selectivity for sulfinate formation may thus well be observed.

[15] Additionally, during our experimental study of this reaction, no direct or indirect evidence for cation formation was observed.

[16] See the Supporting Information for the synthesis of **8-*d***.

[17] Control experiments showed that compound **5-*d*** does not reverse back to benzaldehyde and lithiated sulfone. We have also checked that no isotopic scrambling was occurring. See the Supporting Information for details.

[18] See Supporting Information for a detailed discussion of lithium cation positioning.

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