Review

Latest Developments in the Julia-Kocienski Olefination Reaction: Mechanistic Considerations

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Latest Developments in the Julia-Kocienski Olefination Reaction: Mechanistic Considerations

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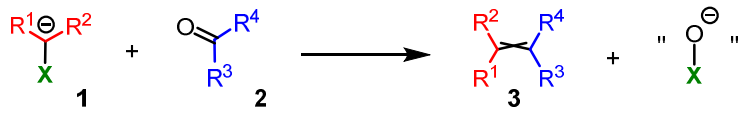
Abstract: The Julia-Kocienski olefination reaction has become over past 30 years since its discovery one of the key C-C connective methods that is used in the late-stage natural product synthesis. The reaction proceeds under mild reaction conditions, with wide substrate scope and functional group tolerance, and with high (*E*) selectivity. In this review, we discuss the reaction from a mechanistic point of view and disclose key features that play an important role in reaction selectivity. Finally, the mechanistic aspects of the newly developed modification of the Julia-Kocienski reaction, which allows the formation of both (*E*) and (*Z*) olefins, from the same reaction partners, are discussed.

Keywords: Julia-Kocienski reaction; olefination; reaction selectivity; reaction mechanism

1. Introduction

Alkenes belong to a chemical functional group that is omnipresent in literally all natural products. Interestingly, since the early times when organic synthesis slowly became a 'useful' scientific discipline, many synthetic strategies have focused on the stereoselective synthesis of these structural motives. Especially, methods that allow for the connective stereoselective introduction of the olefin moiety have become very valuable tools for this achievement. Over the past 100 years, many different connective olefination methods have been developed, but many of them follow the same retrosynthetic pathway [1] - they are based on the reunion of α-negative charge stabilizing reagents **1** with aldehydes or ketones **2** (Table 1).

Table 1. Common carbonyl-based olefination methods used in organic synthesis.



Activating unit X	Olefination Method	Litt. reference
$PhSO_2$	Julia-Lythgoe	Ref.[1]
$ActSO_2$	Julia-Kocienski	Ref.[1]
PhSO(NMe)	Johnson	Ref.[2]
R_3P^+	Wittig	Ref.[3]
$R_2P(=O)$	Wittig-Horner	Ref.[3]
$(RO)_2P(=O)$	Horner-Wodsworth-Emmons (HWE)	Ref.[4]
R_3Si	Peterson	Ref.[5]
R_2B	Boron-Wittig	Ref.[6]

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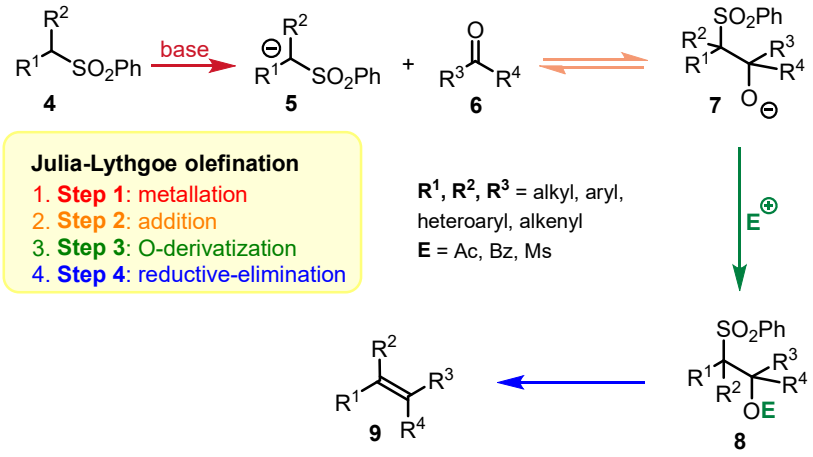
Since the introduction of the Wittig reaction[7,8] in the late 1950s of the twentieth century, Wittig,[3] Horner-Wadsworth-Emmons,[4] Johnson,[2] Peterson,[5] and Julia olefination[1] established themselves as the most widely used olefination protocols. Each of these methods has, of course, its advantages and drawbacks that change over time because each of the methods went through a long and interesting development since its original disclosure. In this review, we wish to focus on the so-called modified Julia reaction,[1,9–16] also known as the Julia one-pot, Silvestre-Julia, or Julia-Kocienski olefination, and its development in terms of the reaction mechanism and selectivity.

2. Origins and Mechanism of the Julia-Kocienski Olefination Reaction

2.1. Julia-Lythgoe Olefination vs. Julia-Kocienski Olefination: A Comparison

Classical Julia olefination, also known as Julia-Lythgoe olefination, was described for the first time in 1973 by (Mark) Julia and Paris[17] and was later developed by Kocienski and Lythgoe[18]. The original protocol was soon expanded for the beneficial *O*-derivatization step and thus consisted of four distinct stages carried out commonly in the two-pot protocol (Scheme 1): (1) metalation of an alkylarylsulfone **4**, (2) addition of the resulting carbanion species **5** to an aldehyde or ketone **6**, (3) *O*-acylation (sulfonylation) of the adduct **7**, and (4) reductive-elimination of the β-acyl (sulfonyl) oxysulfone **8** intermediate. The addition of **5** to **6** typically yields product **7** as a mixture of all possible diastereoisomers; however, this is not of consequence because the stereochemical information encoded in **7** (or **8**) is lost during the reductive elimination step. A common feature of Julia-Lythgoe olefination is its high (*E*)-stereoselectivity[1] – a consequence of the various radical mechanisms that operate in the final stage of reductive elimination[19].



Scheme 1. Julia-Lythgoe olefination protocol.

The main drawbacks of Julia-Lythgoe olefination, namely the steric requirement-driven (*E*/*Z*)-selectivity, and the two-pot protocol, were in 1993 overcome by Silvestre Julia[20,21] (brother of Mark Julia). Their modification of the standard Julia-Lythgoe olefination protocol was based on the replacement of the phenylsulfonyl group with the benzo[*d*]thiazol-2-ylsulfonyl (BT) group (Scheme 2). The common feature of the new transformation with Julia-Lythgoe olefination are the first two steps: (1) metalation and (2) addition of metalated sulfone **11** to aldehyde **12**. Since in this case the aryl group in the alkyl aryl sulfone is an electron-acceptor, the initially generated *β*-alkoxy sulfone adduct **13** can undergo to spontaneous Smiles rearrangement (S to O migration of the heteroaryl group) to yield adduct **15**. Subsequent *β*-elimination of SO_2 (**18**) and of an aryloxide anion (**17**) in **15** directly forms olefin **16**.

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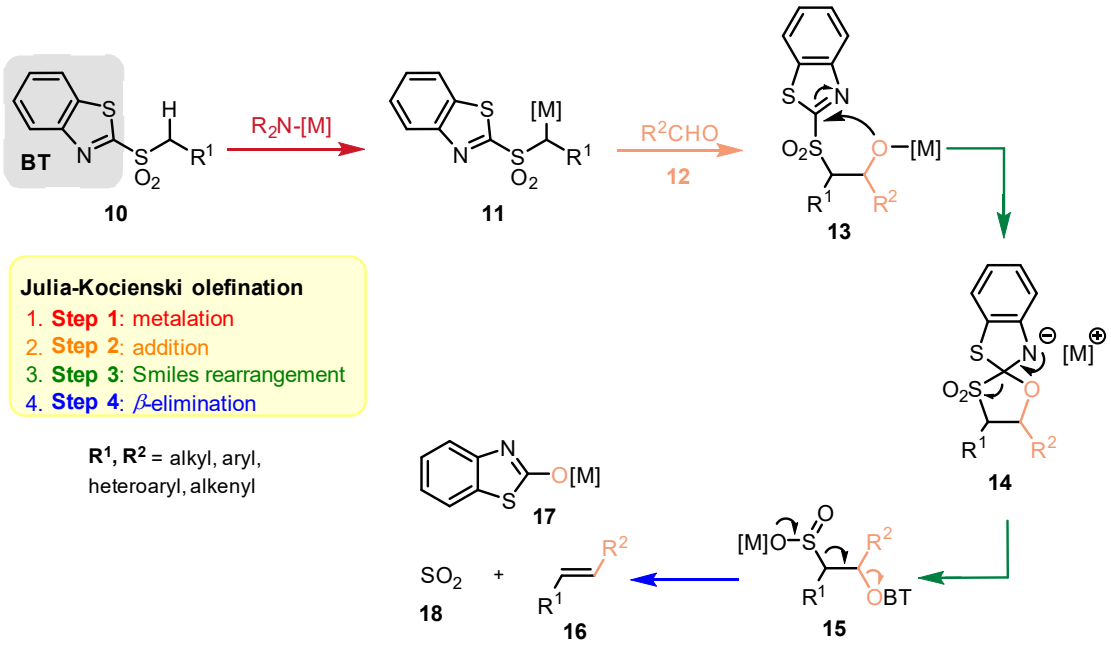

Scheme 2. Julia-Kocienski olefination reaction – mechanistic overview.

As mentioned above, Silvestre Julia introduced the BT-group as the only electron-acceptor aryl group suitable for the Julia-Kocienski olefination reaction. But this situation did not last long, and many other research groups introduced several different heteroaryl groups such as pyridine-2-yl (**PYR**),[20,22] 1-phenyl-1H-tetrazole-5-yl (**PT**),[23] 1-tert-butyl-1H-tetrazole-5-yl (**TBT**),[24] and 3,5-bis(trifluoromethyl)phenyl (**BTFP**)[25] and others[20,26]. Interestingly, only the **PT** group introduced by Kocienski *et al.*[13,24] possessed sufficiently interesting properties (diminished side reactions such as homocoupling[13], high (*E*)-selectivity) that remained along with the original BT group as the most widely used heteroaryl acceptor groups explored in olefination reactions.

The generalized scopes and limitations and the achieved (*E*/*Z*) selectivities observed for Julia-Lythgoe and Julia-Kocienski olefination are summarized in Table 2.

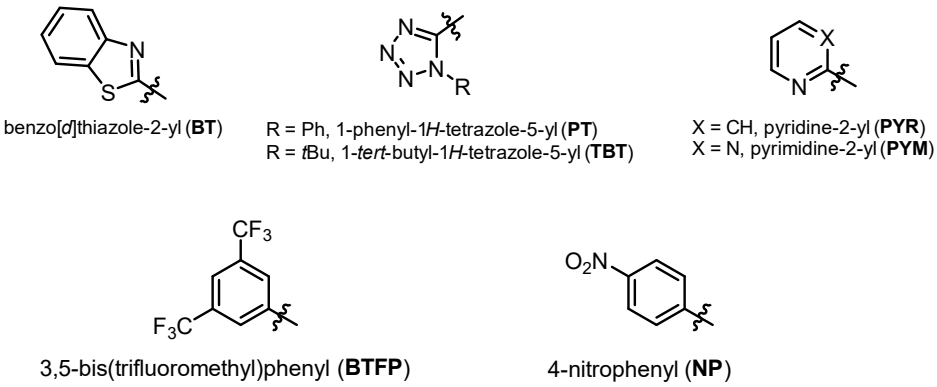

Figure 1. Most commonly used activators in Julia-Kocienski olefination.

Table 2. Comparison of the Julia-Lythgoe and Julia-Kocienski olefination: General features.

Key Features	Julia-Lythgoe	Julia-Kocienski
Practical Difference	*Two-pot protocol*	*One-pot protocol*
Origin of Stereoselectivity	*Reductive Elimination Step*	*The addition step*
Scope of olefin formation		
Terminal	✓	✓
1,2-disubstituted	✓	✓

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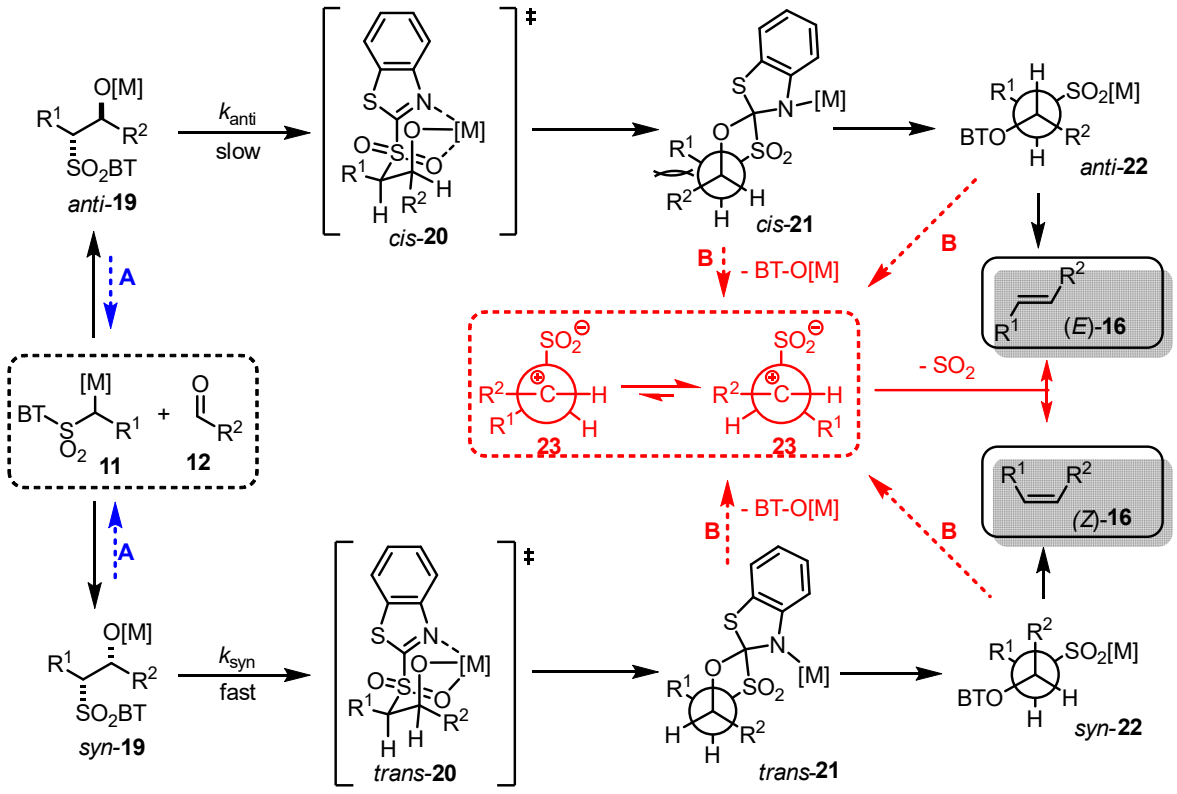
Trisubstituted	✓	≈
Tetrasubstituted	≈	X
Scope of (*E*)-Stereoselectivity		
1,2-disubstituted	✓	✓
Trisubstituted	≈	X
Tetrasubstituted	≈	X
Scope of (*Z*)-Stereoselectivity		
1,2-disubstituted	X	✓ *if the TBT-activating group is used;*
Trisubstituted	X	X
Tetrasubstituted	X	X

✓ – good to excellent; ≈ – acceptable; X – unsatisfactory result(s).

2.2. Reaction Mechanism and Its Impact on the Selectivity of Julia-Kocienski Olefination

The Julia-Kocienski reaction mechanism was intensively studied by Silvestre Julia[20,21] and the study was further extended by P. Kocienski and R. Blackmore.[11–13,24] Based on these excellent mechanistical works, the reaction mechanism could be established with respect to the stereochemical outcomes of the reaction (Scheme 3). There are three important features of this mechanism that deserve a brief comment.



Scheme 3. Detailed reaction mechanism of the Julia-Kocienski reaction.

(1) The addition step of metalated sulfone **11** to aldehyde **12** can provide *anti*-adduct *anti*-**19** via **TS1** or *syn*-adduct *syn*-**19** via **TS2** (Figure 2). The selectivity in this step is extremely important since

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all subsequent transformations of intermediate **19**, Smiles rearrangement and *β*-elimination, are stereospecific. Thus, the *syn*/*anti*-selectivity of the addition step determines the final (*E*/*Z*)-olefin ratio. Therefore, in theory, the (*E*/*Z*)-selectivity of the reaction could be swapped from (*E*) to (*Z*) if proper reaction conditions are applied.

(2) When stabilized metalated sulfonyl anions **11** (R^1 = Ph, alkenyl, etc.) are used, the addition step of **11** to **12** becomes reversible (Scheme 3, path A). In this case, the original kinetically driven *syn*/*anti*-ratio of adduct **19** becomes less important in comparison with the Smiles rearrangement reaction rates (transformation of **19** to **22**). In such cases, the rearrangement of *anti*-**19** adduct leading to (*E*)-olefin **16** is slower compared to the rearrangement of *syn*-**19** to olefin (*Z*)-**16** due to repulsive 1,2-interactions in the transition state (see *cis*-**20**).

(3) For the elimination step, two borderline mechanisms are generally accepted. In the first, which is the most common, the rearranged intermediate **22** undergoes *β*-elimination. The elimination is stereospecific, and the *syn*-**19** adduct rearranged intermediate *syn*-**22** furnishes (*Z*)-olefin and the *anti*-**19** adduct rearranged intermediate, compound *trans*-**22** (*trans* refers to the arrangement of R^1 and R^2 within the intermediate cycle), yields (*E*)-olefin. Alternatively, when (hetero)aryl aldehydes **12** (R^2 = (hetero)aryl) an alternative elimination pathway (path B) was postulated to occur. In this case, the elimination pathway should proceed through the formation of intermediate carbocation **23.** The steric requirements of R^1 and R^2 then play a crucial role in the final (*E*/*Z*)-selectivity of the reaction. Path B was used to explain the unexpected (*E*)-selectivity of the coupling reactions carried out using (hetero)aryl aldehydes **12** as substrates.

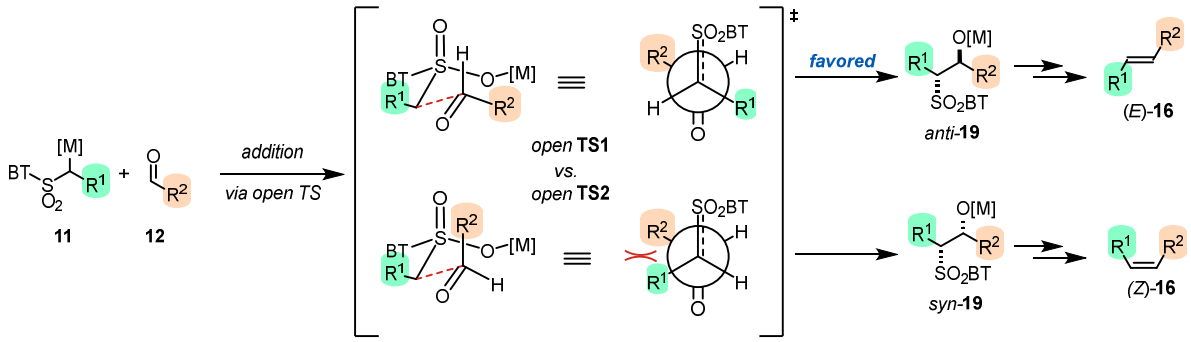

Figure 2. Addition of the metalated sulfone **11** to aldehyde **12**. Mechanistic rationale.

Recently, our group, in collaboration with Robiette's group, proposed an alternative explanation for the observed (*E*) selectivity of these reactions. Our explanation is based on a combined experimental and theoretical study that revealed that the key role in the elimination step plays the rearrangement product **22a** (Scheme 4).[14] In general, both the *anti* and *syn* intermediates **22a**, can adopt the *cisoid* and *transoid* conformation. Conformational equilibrium is strongly influenced by the steric requirements of the R^1 and Ar groups, and in the case of the *anti*-**22a** intermediate, the *transoid* is preferred, while in the case of *syn-22a,* the *cisoid* is preferred. Advanced experimental and theoretical study then suggested that in the case of a *cisoid* conformation, competitive *syn* elimination can occur,[14] explaining almost exclusive formation of (*E*)-olefins observed in the case of olefins of general structure **16a**.

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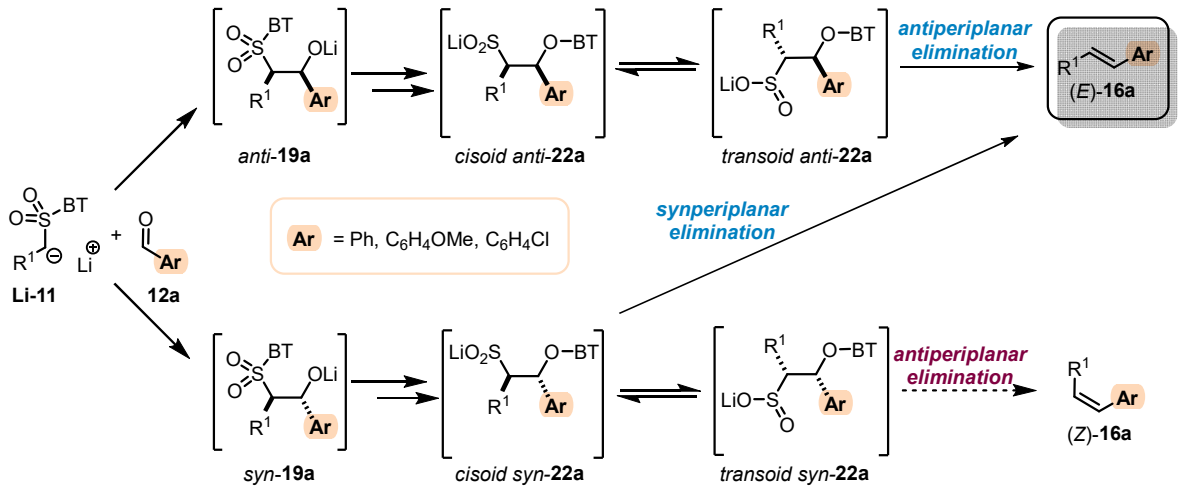
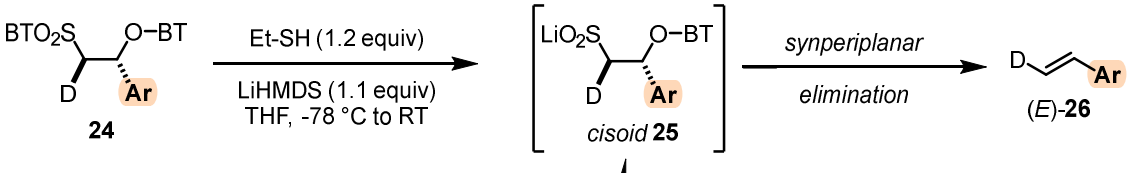


Scheme 4. The rationale for the observed high (*E*)-selectivity in the Julia-Kocienski olefination of aromatic aldehydes.

Theoretical studies also suggested that the *syn* elimination process should be more favored when the aryl substituent R^2 has electron-donating substituents and disfavored when an electron-deficient substituent is present. The postulated prediction was then evaluated using a stereodefined intermediate **24** that was selectively transformed in situ to the corresponding lithiated anion **25** that was allowed to undergo an elimination process. The generated anion cannot undergo the retroaddition process (it is an intermediate after the rearrangement step) and the nucleophile generated in situ (thiolate anion) is not basic enough to trigger the epimerization process of any of the two epimerizable stereogenic centers. Thus, only (*Z*) olefin (*Z*)-**26** should be produced as the main product of the transformation. If the reaction should proceed through the carbocation-type intermediate of the **23** type (see Scheme 3), an approximately 50:50 ratio of the (*E*/*Z*)-isomeric mixture was expected. In all tested cases, the (*E*)-isomer (*E*)-**26**, the product of the *synperiplanar* elimination process was produced as the main product of the reaction, strongly suggesting that the *syn* elimination process is the main process that operates during the Julia-Kocienski olefination reaction of alkyl sulfones with aryl aldehydes. The observed stronger preference for electron-donating group containing intermediates to undergo preferentially *synperiplanar* elimination was also in agreement with the DFT calculation-based prediction.



Entry	Ar	Olefin	Yield [%]	*E*/*Z* ratio
1	4-ClC$_6$H$_4$	**25a**	89	81:19
2	C$_6$H$_5$	**25b**	92	90:10
3	4-MeOC$_6$H$_4$	**25c**	87	94:6

Scheme 5. Stereoselectivity in the elimination step: a competition between the *synperiplanar* and *antiperiplanar* elimination processes.

2.3. Recent Achievements in the Reaction Selectivity Improvements

Reaction mechanism studies carried out by S. Julia and P. Kocienski, which were later confirmed by our own studies, implies that the reaction selectivity is directly linked with the initial *syn*/*anti*-selectivity of the addition step. The adduct ration further directly influences the selectivity (*E*/*Z*) of

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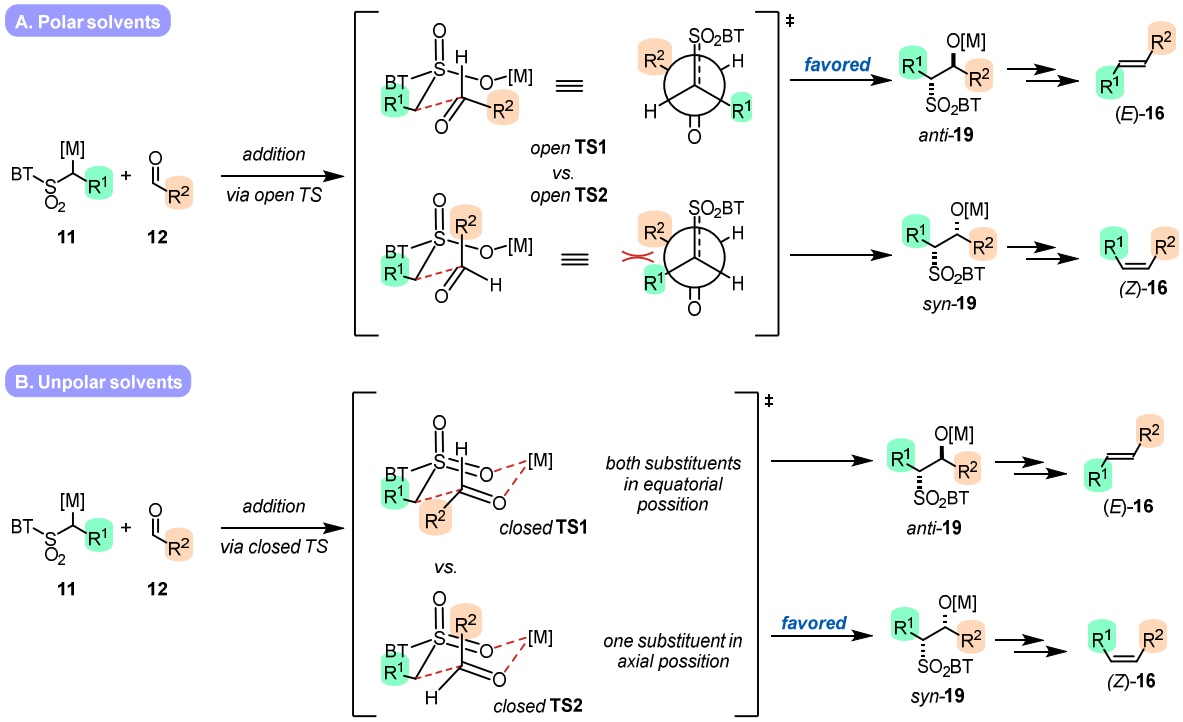
the overall reaction regardless of whether the reaction proceeds through the *antiperiplanar* elimination (for R^1 and R^2 = alkyl), or mixed *antiperiplanar* and *synperiplanar* (for R^1 and/or R^2 = (hetero)aryl) elimination in the final step. Not surprisingly, then, most of the methods developed to influence the reaction selectivity in favor of one of the two isomers focus on the key addition step.

2.3.1. Solvent Effect

The most important and most straightforward way to influence the *syn*/*anti*-selectivity of the addition step is to choose the right solvent for the transformation. When polar solvents such as THF, DME, or DMF are used, *anti*-adduct *anti*-**19** is the preferred product of the addition due to solvent stabilization (Scheme 6A). On the contrary, when nonpolar solvents such as toluene are used, the reaction proceeds via a *closed* transition state (Scheme 6B) and *syn* adduct *syn*-**19** is preferred.



Scheme 6. The impact of the solvent polarity on the stereochemical outcome of the Julia-Kocienki reaction.

It should be noted that, even though such an approach is generally applicable and correct, the role of the solvent might be altered by several factors that cannot be removed from the reaction mixture and which will be discussed in the following two sub-sections.

- **Metal cation**

The metal cation, which is always present in the reaction mixture as a 'residue' after the deprotonation step, has a key influence on the selectivity of the reaction. In general, cations with the character of a hard Lewis acid such as, e.g., Li^+ favor the formation of the (*E*) olefins. It is assumed that the observed (*E*) selectivity is caused by a better stabilization of the generated anion **11** that can further add due to its lower reactivity to the aldehyde **12** with a better selectivity that favors the *anti*-adduct *anti*-**19**. On the contrary, when a large cation is used, such as K^+, the reaction can proceed preferentially either via *closed* TS or the solvent can increase the dissociation of the cation from the anion **11** and thus increase the reactivity of it. The first case is typical for nonpolar solvents (e.g., toluene), since the solvent does not provide additional stabilization to the reagents and/or reaction intermediates. In the latter case, dissociation of the cation from reagent **11** increases the reactivity of the anion and leads to the faster production of the kinetic product of the addition step, *anti*-isomer *anti*-**19**. However, it should also be noted that an increase in anion **11** reactivity can also inevitably

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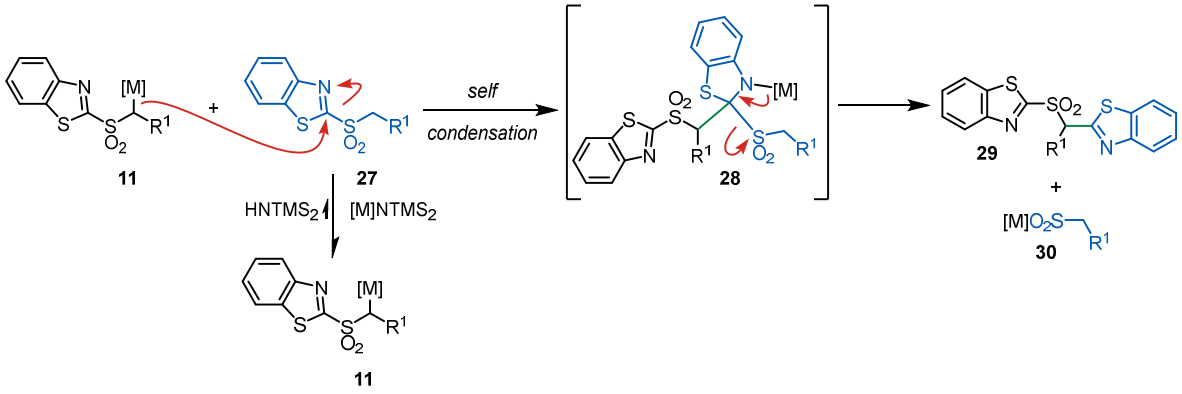
lead to the undesired self-dimerization of reagent **11** (Scheme 7); thus, a compromise between selectivity and reactivity has to be searched.



Scheme 7. Self-condensation reaction that accompanies the reaction of anion **11**.

- **Co-solvents**

The addition of the co-solvents to the reaction mixture can also be beneficial when (*E*)-selectivity is searched. It was observed that the addition of co-solvents such as DMPU or HMPA to the reaction mixtures carried out in the THF or DMF leads to an increase in the (*E*)-olefin selectivity of the desired product. It is believed that the co-solvent role is in metal cation scavenging with an impact similar to that described in the previous section (increased reactivity that favors the *anti*-adduct formation).

2.3.2. Additives

Another way to increase the (*E*/*Z*) selectivity of the Julia-Kocienski reaction is the addition of additives to the reaction mixture. Over the years, many various additives have been used for such purposes; however, only a few of them have had a significant effect. The relevant ones are listed below.

- **Crown ethers**

As mentioned in the previous section, the role of (co-)solvent was shown to have a tremendous effect on the reaction yield and selectivity. As a *modus operandi*, it was postulated that polar solvents increase the reactivity of anion **11** due to a cation/anion separation (reaction kinetic) that leads to the preferential formation of *anti*-adduct (polar solvents) or *syn*-adduct (nonpolar solvents). As a disadvantage, self-condensation of metalated sulfone **11** (Scheme 7) was observed. The use of specific cation-chelating co-solvents such as HMPA or DMPU met only with limited success even though in several cases it led to the diminished formation of self-condensation products and an increase in the (*E*) selectivity.

Based on the same logic, to increase the reactivity of metalated sulfone **11** and thus increase *anti*-adduct formation (kinetic product), an excess of crown ethers (18-crown-6 for K^+; 12-crown-6 for Li^+)[27] can be used during the reaction as demonstrated in several recent total syntheses of natural products (*e.g.*, zeaenol,[28] paecilomycins E and F,[29] amphidinolide E,[30] and salarins A and C[31]).

However, it should be noted that if metalated sulfone **11** is used with a group in the lateral chain (R^1) that is capable of stabilizing the generated anion, the addition of generated anion **11** to aldehyde **12** is reversible. Consequently, the *syn*/*anti*-ratio of adducts **19** is in equilibrium and (*Z*)-olefin (*Z*)-**16** is formed preferentially due to a faster ($k_{anti} < k_{syn}$) Smiles rearrangement step.[32]

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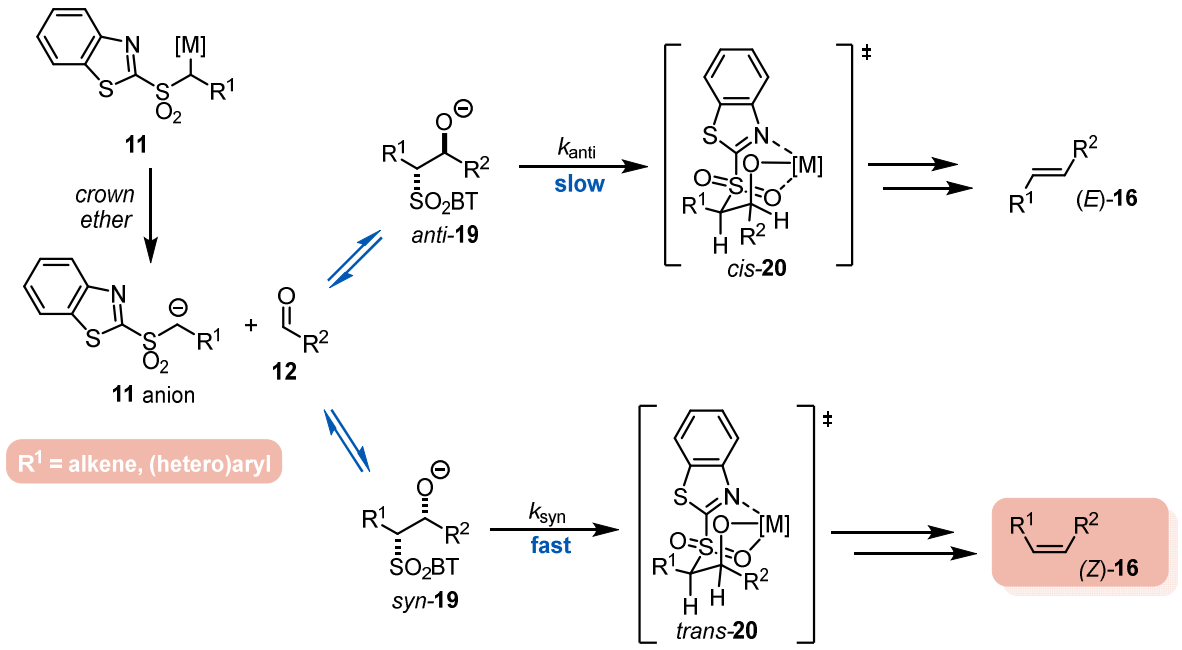

Scheme 8. Role of crown ethers in the Julia-Kocienski reaction. High (*Z*)-selectivity in the case of stabilized metalated sulfones.

- **Ammonium salts**

The use of ammonium salts proved to be also beneficial and in several cases of highly complex molecular scaffolds led to an increase in the observed reaction yield and (*E*)-selectivity.[33,34] It is believed that the role of ammonium salts is in the activation of aldehyde **12**, where, due to its steric requirements, increases the *anti*-selectivity of the addition step. It should also be noted that the role of counter anion of the ammonium salt is not innocent. The best (*E*) selectivity was observed when potassium-containing metalated sulfone **11** was reacted in the presence of TBAB (*tetra*-butylammonium bromide) and lithium-containing metalated sulfone **11** was reacted in the presence of TBAC (*tetra*-butylammonium chloride). Such observations suggest the beneficial formation of KBr and LiCl salts during the reaction.

- **Chelating Metals**

Similarly, metal cations as e.g., $CeCl_3$,[35,36] $MgCl_2$,[37] $ZnCl_2$, and LiBr, can be used to activate aldehyde **12** during the reaction. The addition of such salt generally results in an increase in the reaction yield of the transformation. The (*E*/*Z*) selectivity of the transformation is influenced only if aldehydes bearing *α*-alkoxy substituents[37] are used in the presence of an excess of $MgCl_2$ or $ZnCl_2$ (addition via the Cram-chelate transition state).[38]

3. Julia-Kocienski Olefination – Extension to Carboxylic Acid Derivatives

All the above-mentioned olefination methods are based on the reunion of the metalated sulfone **11**-type intermediate and a carbonyl-containing intermediate **12** (Scheme 2). The overall transformation can thus be regarded as an addition/rearrangement/elimination sequence, where the final (*E*/*Z*)-selectivity of the newly olefinic bond is determined by the addition step. Therefore, the stereoselectivity is dictated by the reaction kinetic of the addition step (kinetic conditions) or by the kinetic of the rearrangement step (the addition step is in equilibrium) (Scheme 3).

However, recently this paradigm changed since we have introduced 'reaction work-up driven selectivity' for the Julia-Kocienski reaction.[39] In analogy to the famous Peterson olefination reaction,[5] we have designed and optimized the new Julia-Kocienski protocol that allows the selective (*E*) or (*Z*) olefin formation by a simple change in the reaction work-up procdure. Our protocol is based on the seminal work of Jørgensen et al.[40,41] that demonstrated that *β*-keto BT

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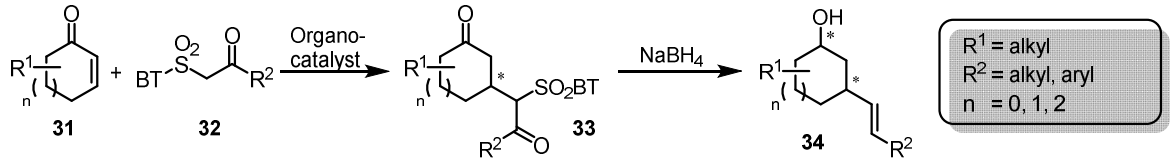
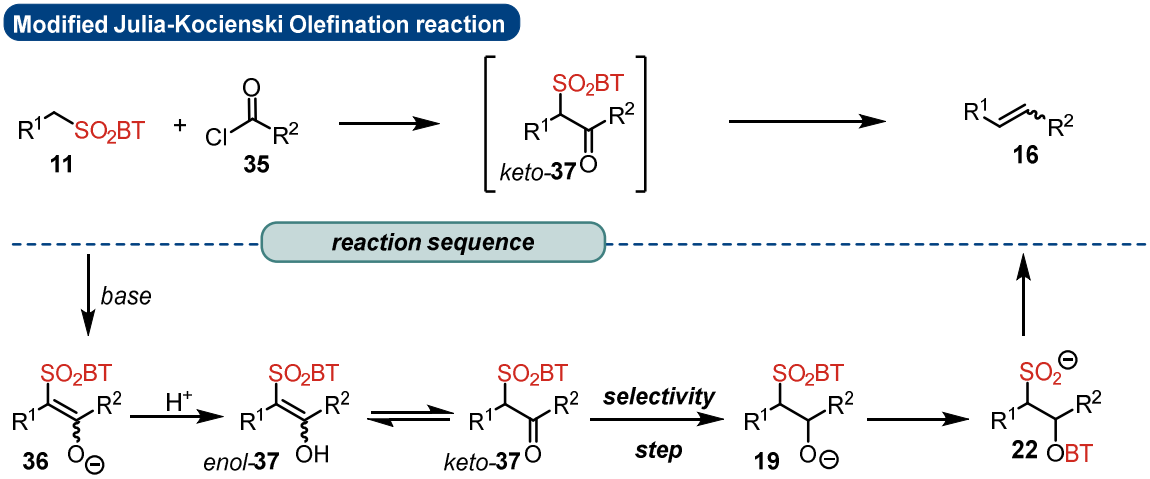
sulfones **33** can be successfully transformed into the corresponding olefins **34** in high yields and (*E*)-stereoselectivity.



Scheme 9. A seminal work by Jørgensen et al. [40,41] that demonstrated the possibility of stereoselective transformation of *β*-keto sulfones into the corresponding (*E*)-olefins **34**.

On the basis of these results, we have designed a novel type of the Julia-Kocienski reaction that allows the synthesis of the desired olefins **16** starting from the metalated sulfone **11** and acyl halides **35** (Scheme 10). In this sequence, the reunion of the two reagents (compounds **11** and **35**) is carried out using previously described protocol.[42,43] The generated adduct **36** is then quenched in situ with the external source of the proton (protic solvent, e.g., MeOH) and *β*-keto sulfone **36** is formed. Compound **36** is present in the reaction mixture as a dynamic mixture of its keto and enol derivatives. Compound **36** is present in the reaction mixture as a dynamic mixture of its keto and enol derivatives. When an external mild reducing agent (e.g., $NaBH_4$) is added, the keto-form of *keto*-**36** is selectively reduced, and the nucleophilic hydride approach is directed according to the Felkin-Ahn model[44] (Scheme 11). Carbonyl reduction preferentially generates a *syn* derivative of β-hydroxy sulfone *syn*-**19**, and compound *syn*-**19** is further converted via the Smiles rearrangement/*β*-elimination sequence of the Julia-Kocienski olefination reaction to olefin (*Z*)-**16**. However, if chelating salts such as $ZnCl_2$ are added to the reaction mixture prior to $NaBH_4$, the reduction proceeds through the Cram-chelate model and the *anti*-*β*-hydroxy sulfone *anti*-**19** is formed. Consequently, compound *anti*-**19** furnishes after the Smiles rearrangement/*β*-elimination sequence (*E*)-olefin (*E*)-**16**.



Scheme 10. Proposed reaction sequence for the modified Julia-Kocienski olefination reaction, where the stereoselectivity of the generated olefin is not determined in the addition step.

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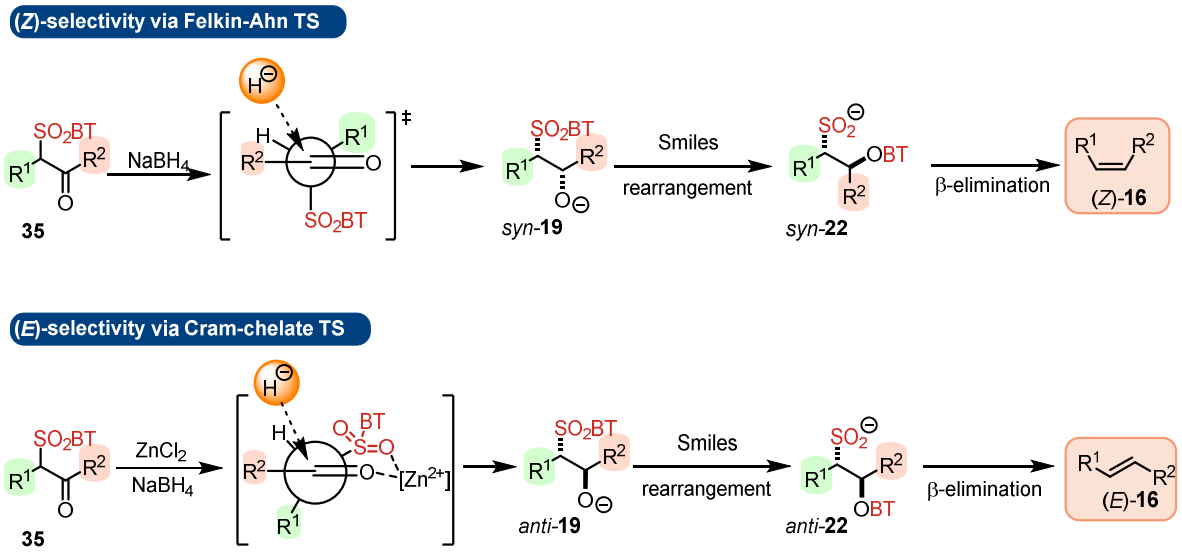

Scheme 11. The rational design behind the stereoselective modified Julia-Kocienski olefination reaction.

Although only preliminary scope and limitations of the transformation were established (28 examples), the method was successfully applied in the context of the (nitro)fatty acid synthesis.[39]

4. Conclusions

Since its first dissemination in 1993 the reaction sequence that is now referred to as the Julia-Kocienski reaction has become very popular late-stage connective method in natural product synthesis, because it combines highly efficient (reaction yield) and selective (predominantly (*E*)-selective) connective method that proceeds in one-pot protocol and under mild reaction conditions and with broad substrate and functional group tolerance. The past 30 years of reaction development have also identified key mechanistic properties that allow better control of reaction selectivity. Moreover, we have recently introduced a novel modification of the Julia-Kocienski reaction that not only increases the starting material scope since it allows for the use of previously inaccessible carboxylic acid derivatives as substrates but also allows for the selective (*E*) or (*Z*)-olefin formation. In addition, this method allows for the first time in the development of the Julia-Kocienski olefination reaction an independent formation of (*E*) or (*Z*) olefins starting from the same starting materials by simple reaction work-up protocol alternation.

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