Tetrahedron Letters 52 (2011) 2348–2352

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Simple protocol for enhanced (*E*)-selectivity in Julia–Kocienski reaction

Jiří Pospíšil *

Institute of Condensed Matter and Nanosciences—Molecules, Solids and Reactivity (IMCN/MOST), Université catholique de Louvain, Place Louis Pasteur, 1 bte 2, 1348 Louvain-la-Neuve, Belgium

ARTICLE INFO

Article history:
Received 26 January 2011
Revised 15 February 2011
Accepted 18 February 2011
Available online 26 February 2011

Keywords:
Julia–Kocienski reaction
Olefins
Selectivity
Chelation

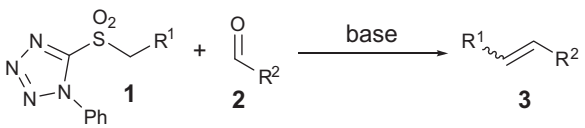
ABSTRACT

A short and efficient Julia–Kocienski olefination protocol, based upon the use of chelating agents (18-crown-6 or TDA-1 for K^+; 12-crown-4 or HMPA for Li^+), was developed. This protocol enhances the (*E*)-selectivity of the reaction and the desired olefins are obtained generally with >10:1 (*E*/*Z*)-selectivity.

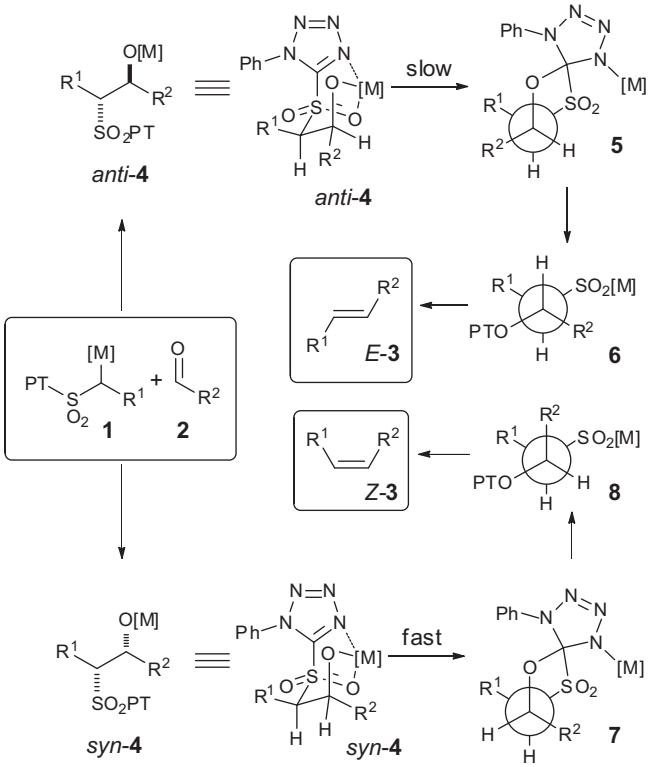
The formation of C=C double bonds is of paramount importance in the field of organic chemistry.[1] The reason for this lies not only in the fact that this structural motif (olefin) is present in various natural and nonnatural bioactive compounds, but also in the fact that olefins can be easily transformed into a wide variety of different functional groups.

Recently, Julia–Kocienski reaction has become a very popular method to achieve the double bond formation thanks to its wide functional group tolerance and possibility to perform the transformation under very mild reaction conditions. As a consequence, this reaction has become one of the most favorite late stage coupling methods used in total synthesis (Scheme 1).[2]

In general, the Julia–Kocienski reaction yields olefins predominantly in (*E*)-configuration on newly formed double bond. However, low, missing, or even inversed selectivity ((*Z*)-isomer formed as the major one) was also observed when the standard reaction conditions were used.



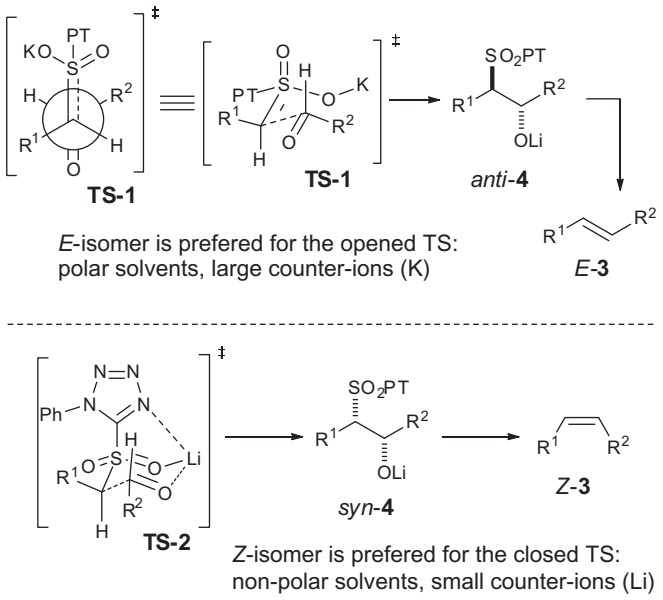
Scheme 1. Julia–Kocienski olefination.



Scheme 2. Proposed mechanism of Julia–Kocienski olefination.

* Tel.: +32 10 472 919; fax: +32 10 472 788.
E-mail address: jiri.pospisil@uclouvain.be

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.02.086



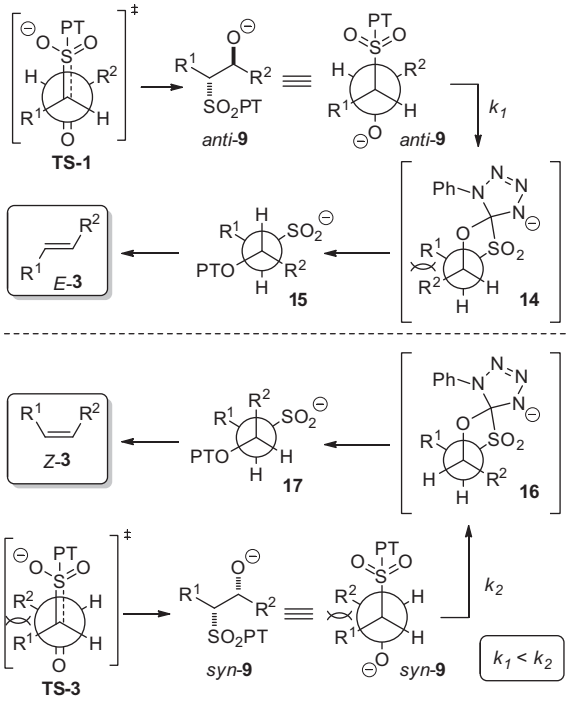
Scheme 3. Proposed guidelines for the reaction selectivity.

For this reason, it became important to postulate some guidelines that would allow us to predict the reaction selectivity. Such guidelines, based on the generally accepted Julia–Kocienski reaction mechanisms[2,3] (Scheme 2), and some additional experimental observations,[4] were proposed (Scheme 3). It was stated that if the addition of aliphatic α-metalated sulfones to aldehydes is a nonreversible process, then the stereochemical outcome of the reaction directly depends upon the *syn*/*anti* selectivity of the addition step.[2,5] By other means, if the addition of α-sulfonyl anion proceeds via an open **TS-1** (K^+-bases/polar solvent), formation of (*E*)-olefin should be observed. Contrary, if a closed **TS-2** (Li^+-bases/nonpolar solvents) is preferred, *Z*-olefins should be obtained.

These statements are based on observations that the rest of the sequence, namely the transformation of the *anti*- and *syn*-**4** adducts to the corresponding olefins **3**, via a Smiles rearrangement/elimination sequence, is stereospecific (Scheme 2).[2,5]

However, there are exceptions to these guidelines. In some cases, the best (*E*)-selectivity (addition via open **TS-1**) was achieved when a Li^+-containing base (LiHMDS) was used in combination with polar solvents (DMF/HMPA).[6,7] Thus, in general, it is difficult to predict with high level of confidence the selectivity outcome of the reaction; this situation being rather inconvenient when the coupling of two complex fragments is desired. Therefore, we decided to develop a new protocol that would allow the Julia–Kocienski reaction to proceed with high (*E*)-selectivity.

We assumed that the addition of selective metal–cation chelating species into the reaction mixture might increase the selectivity

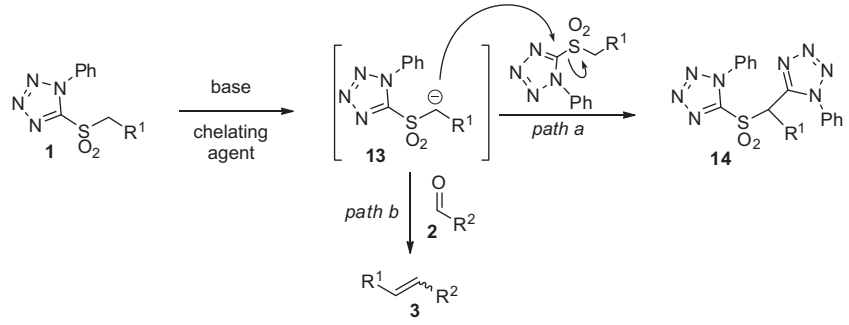


Scheme 5. Addition of anion generated from α-monosubstituted sulfone to aldehyde.

of the transformation. This assumption was based upon the expectation that selective cation chelation will create 'naked' sulfonyl anion **13**. As a consequence, the highly reactive intermediate **13** can either undergo a rapid self-condensation (Scheme 4, path a) or it can react with aldehyde **2** (Scheme 4, path b). To favor the addition (path b) over the self-condensation (path a), the aldehyde has to be added to the reaction mixture rapidly after the base. On the other hand, we have to let some time to the chelating agents to chelate the specific alkali metal cation to generate the more reactive 'naked' carbon-based anion **13**.

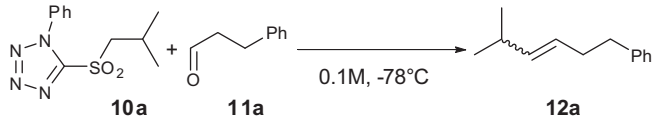
We believe that if we would find good reaction conditions where the chelating agent would have enough time to chelate the corresponding cation but the self-condensation of **13** would be sufficiently slow, then the addition of **13** to aldehyde **2** should proceed via an open **TS-1** to yield adduct *anti*-**9** (Scheme 5). We expect that **TS-1** will be preferred over the other possible open transition state **TS-3**. In **TS-3** the groups R^1 and R^2 suffer from severe steric repulsions. Additionally, we expect that the addition of **13** to aldehyde **2** is an irreversible process, since the retro-addition would form highly unstable 'free' carbon-based anion species.

The presence of a chelating agent should play an important role even after the addition step, since under standard reaction condi-



Scheme 4. Julia–Kocienski reaction in the presence of chelating agents: two plausible competitive pathways.

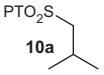
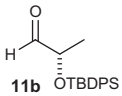
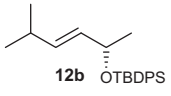
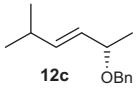
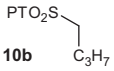
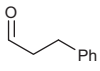
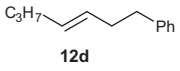
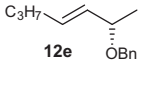
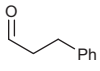
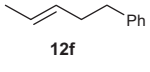
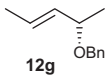
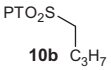
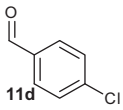
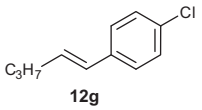
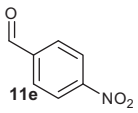
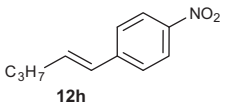
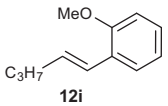
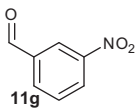
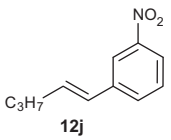
Table 1
Reaction conditions optimization



Entry	Conditions	Solvent	Yield[a]	(*E*/*Z*)[b]
1	KHMDS (1.1 equiv)	THF	88%	4.3:1
2	KHMDS (1.1 equiv), 18-crown-6 (1.1 equiv)	THF	86%	15:1
3	KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	THF	84%	>50:1
4	KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	Toluene	87%	>50:1
5	KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	DMF	78%	>50:1
6	KHMDS (1.1 equiv)	DMF/TDA-1 3:1[c]	83%	>50:1
7	NaHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	THF	78%	4:1
8	NaHMDS (1.1 equiv)	DMF/TDA-1 3:1[c]	81%	4:1
9	LiHMDS (1.1 equiv)	THF	90%	2.1:1
10	LiHMDS (1.1 equiv), 12-crown-4 (2.0 equiv)	THF	79%	3:1
11[c]	LiHMDS (1.1 equiv)	DMF/HMPA 3:1	92%	5:1
12[c]	LiHMDS (1.1 equiv)	DMF/DMPU 3:1	88%	4.4:1

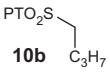
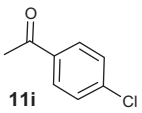
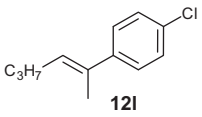
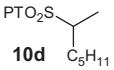
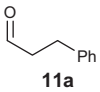
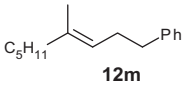
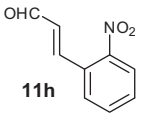
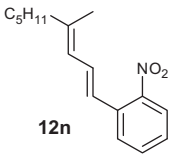
[a] Average of three runs; refers to pure isolated compounds.
[b] Average of three runs; based on crude ^{1}H NMR spectra.
[c] Reaction performed at −60 °C.

Table 2
Preliminary scope and limitations—1,2-disubstituted olefins

Entry	Sulfone	Carbonyl compound	Product	Condition[a]	Yield (*E*/*Z*)
1				A	81% (21:1)
2	**10a**	**11b**	**12b**	B	82% (>50:1)
3				A	78% (19:1)
4		**11c**	**12c**	B	75% (>50:1)
5				A	74% (5:1)
6	**10b**	**11a**	**12d**	B	86% (>50:1)
7				A	68% (9:1)
8		**11c**	**12e**	B	63% (>50:1)
9				A	72% (8:1)
10	**10c**	**11a**	**12f**	B	62% (>50:1)
11				A	76% (4:1)
12		**11c**	**12g**	B	75% (19:1)
13				A	47% (50:1)
14	**10b**	**11d**	**12g**	B	65% (25:1)
15				A	54% (30:1)
16		**11e**	**12h**	B	67% (20:1)
17				A	59% (>50:1)
18		**11f**	**12i**	B	64% (>50:1)
19				A	61% (19:1)
20		**11g**	**12j**	B	74% (10:1)

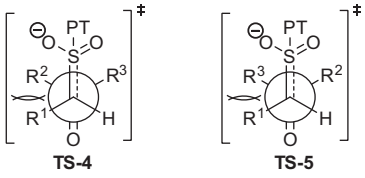
[a] Conditions: (A) KHMDS (1.1 equiv), THF; (B) KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv), THF.

Table 3
Preliminary scope and limitations—trisubstituted olefins

Entry	Sulfone	Carbonyl compound	Product	Condition[a]	Yield (*E*/*Z*)
1	 **10b**	 **11i**	 **12l**	C	Nr
2				D	76% (1.6:1)
3				E	87% (2.6:1)
4				F	73% (2.6:1)
5	 **10d**	 **11a**	 **12m**	C	Nr
6				E	97% (1.2:1)
7		 **11h**	 **12n**	C	Nr
8				E	75% (1.2:1)

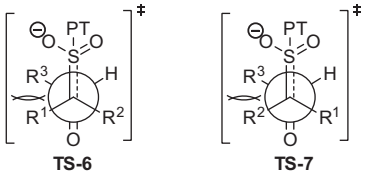
[a] Conditions: (C) KHMDS, various conditions; (D) LiHMDS (1.1 equiv), THF; (E) LiHMDS (1.1 equiv), 12-crown-4 (2.0 equiv), THF; (F) LiHMDS (1.1 equiv), 12-crown-4 (2.0 equiv), toluene.

Addition of anion generated from α monosubstituted sulfone to ketone



Two possible open transition states

Addition of anion generated from α disubstituted sulfone to aldehyde



Two possible open transition states

Scheme 6. Proposed TS for α-monosubstituted sulfones addition to ketones and α-disubstituted sulfones to aldehydes.

tions (reaction performed without the presence of any chelating agent), the adduct *anti*-**9** should undergo the Smiles rearrangement only very slowly (due to the steric repulsion between R^1 and R^2 as showed in adduct *anti*-**4**, see Scheme 2). In our case, the rearrangement of adduct *anti*-**9** should proceed with faster reaction rate due to enhanced nucleophilic character of alkoxide anion. Similarly, the fragmentation of intermediate **15** should proceed faster than when chelating agents are not used.

To test our hypothesis, the olefination reaction of sulfone **10a** with aldehyde **11a** was investigated (Table 1).[8] Under the standard reaction conditions (KHMDS used as a base); the desired olefin **12a** was obtained in 88% yield with a 4.3:1 (*E*/*Z*)-selectivity (Table 1, entry 1). However, when the reaction was performed in the presence of 1.0 equiv of 18-crown-6, olefin **12a** was isolated in 86% yield and with a greater than 15:1 (*E*/*Z*)-selectivity (Table 1, entry 2). Further increase in 18-crown-6 loading yielded alkene **12a** in comparable yield and with an excellent >50:1 (*E*/*Z*)-selectivity (Table 1, entry 2). Interestingly, no solvent effect was observed on the reaction selectivity (Table 1, entries 3–5). Additionally, TDA-1[9] was used as 18-crown-6 surrogate, yielding olefin **12a** in excellent yield and exquisite (*E*/*Z*)-selectivity (Table 1, entry 6). In all these experiments, aldehyde **11a** was added 0.5 min after the base (to avoid the undesired self-condensation reaction).

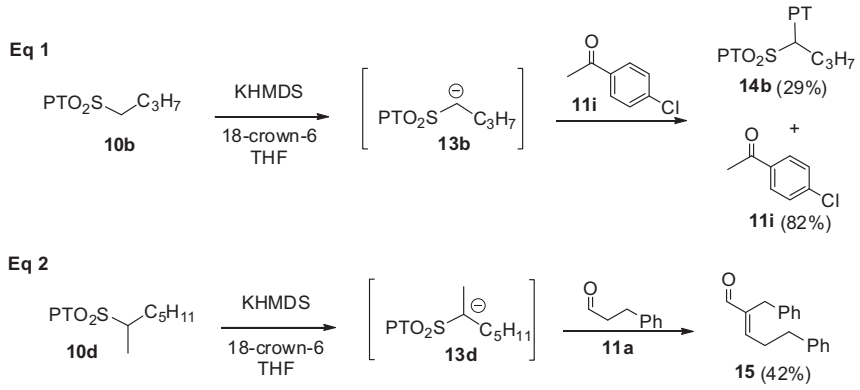
Control experiments to clarify if the 18-crown-6 and the TDA-1 behave as K^+ scavengers were also performed. First, we replaced KHMDS in the standard reaction conditions set (KHMDS/18-crown-6/THF or KHMDS/DMF:TDA-1 = 3:1) with NaHMDS (Table 1, entries 7 and 8). As expected, the (*E*/*Z*)-selectivity of both reactions dropped and the original 4:1 (*E*/*Z*)-ratio was recuperated (Table 1, entry 1).

Additionally, the olefination reaction between sulfone **10a** and aldehyde **11a**, promoted by LiHMDS, was investigated (Table 1, entries 9–11). As expected, the addition of 12-crown-4 (Table 1, entry 10) or HMPA as a co-solvent (Table 1, entry 11) increased the (*E*)-selectivity of the coupling, but the influence of these additives was less pronounced when compared with the KHMDS/18-crown-6 system. We believe that this is due to a slower chelation of the Li^+ cation by 12-crown-4 or HMPA when compared to the K^+/18-crown-6 system.[10]

Having optimized the reaction conditions, the preliminary scope and limitations of our protocol were established (Tables 2 and 3). First, the (*E*/Z)-selectivity of 1,2-disubstituted olefins prepared from linear or β-branched sulfones **10a–c** reacting with linear and/or α-substituted aldehydes **11a–c** under our reaction conditions were examined (Table 2, entries 1–12). In all studied cases, the olefins **12b–g**, that were prepared using KHMDS/18-crown-6 conditions, were furnished with very good to excellent (*E*)-selectivity. It is important to note that the observed (*E*/*Z*)-selectivities were always superior to those obtained under the classical reaction conditions (KHMDS/THF).

Next, the reaction of sulfone **10b** with aromatic aldehydes **11d–g** was examined (Table 2, entries 13–20). Surprisingly, in these cases, the (*E*/*Z*)-selectivity of the olefin formation was worse if the chelating agents were used. On the other hand, the reaction yields were in general 10% higher.

Finally, the stereoselective synthesis of trisubstituted olefins was attempted (Table 3). First, the reaction between α-monosubstituted sulfone **10b** and ketone **11i** was attempted (Table 3, entries 1–4). Interestingly, if KHMDS was used as a base, the formation of olefin **12l** was not observed. In contrast to this result, the use of LiHMDS provided the desired olefin **12l** in very good yield (Table 3, entries 2–4). The same situation occurred if α-disub-



Scheme 7. Side products obtained during the KHMDS-mediated attempts of trisubstituted olefin synthesis.

stituted sulfone **10d** reacted with aromatic or aliphatic aldehyde **11h** or **11a** (Table 3, entry 5). Also in this case, the use of LiHMDS as a base furnished the desired olefins **12m** and **12n** in good to excellent yields (Table 3, entries 6 and 7). In all these cases, very low or virtually missing (*E*)-selectivity was observed. We believe that the missing selectivity can be attributed to the fact that both possible open transition states, by which the reaction can proceed, suffer from rather severe steric restrictions (Scheme 6).

As shown in Table 3, if the synthesis of trisubstituted olefins via Julia–Kocienski olefination reaction was attempted under our KHMDS/18-crown-6 or KHMDS/TDA-1 conditions, no olefin formation was observed (Scheme 7). In all cases, only the products of sulfone self-condensation (product **14**) or aldol condensation reaction (compound **15** if aldehyde was used as the coupling partner), were obtained. It was suggested that the formation of these undesired products might be caused either by the low reactivity of the electrophilic partner (ketone vs aldehyde) or by the steric hindrance presented around the generated anion. In both cases, the addition of anion **13b** to ketone **11i** (Scheme 7, Eq. 1) or of anion **13d** to aldehyde **11a** is kinetically less favored than the addition of anion **13b** to aldehyde **11a** (Scheme 7, Eq. 2) due to steric reasons. As a consequence, a competitive deprotonation of α-carbonyl hydrogens might occur. The protonated sulfonyl species then might easily undergo the self-condensation reaction with another molecule of metalated sulfone **10**.

The same is true, of course, if LiHMDS is used as a base. However, in this case, the Li^+ cation presumably serves as a Lewis acid that activates carbonyl group and, therefore, facilitates the addition of generated lithium sulfonyl anion.

In conclusions, new conditions for the Julia–Kocienski olefination, that use specific metal cation chelating agents to enhance the reaction's (*E*)-selectivity, were developed.[11] Even though the exact role of chelating reagents is not clear at the moment and requires further investigation, we believe that this new modification of the standard olefination reaction will find a wide application in the synthesis of complex natural products.

Acknowledgments

J.P. is grateful to Professor István E. Markó (Université catholique de Louvain) for his continuous support. Financial support of this work by the Université catholique de Louvain and the Fond de la Recherche Scientific (Chargé de Recherche F.N.R.S.) is gratefully acknowledged.

Supplementary data

Supplementary data (full experimental details and characterization data of synthetic compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.086.

References and notes

1. (a) Dumeunier, R.; Markó, I. E. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 104–161; (b) Kocienski, P. J. In *Comp. Org. Synth.*; Trost, B. M., Fleming, I., Eds., 1991; 6, pp 987–1000.
2. (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585; (b) Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831–1844. and references cited therein..
3. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357; (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878; (c) Kocienski, P. J.; Bell, A. G.; Blakemore, P. R. *Synlett* **2000**, 365–366.
4. Blakemore, P. R.; Cole, W. J.; Kociensky, P. J.; Morley, A. *Synlett* **1998**, 26–28.
5. Markó, I. E.; Pospíšil, J. In *Science of Synthesis*; de Meijere, A., Ed.; Georg Thieme Verlag KG: Stuttgart, 2010; pp 105–160.
6. (a) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773; (b) Albrecht, B. K.; Williams, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11949–11954.
7. It was also reported that the addition of 18-crown-6 (for KHMDS promoted coupling) might increase the reaction selectivity if an α *O*-alkyl substituted aldehyde was used as a reaction substrate. It was suggested that the presence of 18-crown-6 disabled possible stabilization of the adduct and so, prevented the retro addition reaction. Ishigami, K.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2005**, *61*, 7546–7553.
8. For complete reaction optimization table see Table S-1.
9. TDA-1 = tris[2-(2-methoxyethoxy)ethyl]amine; selective K^+ chelating agent, see e.g. Tamao, K.; Nakagawa, Y.; Ito, Y. *Org. Synth.* **1996**, *73*, 94–109.
10. (a) Bradshaw, J. S.; Izatt, R. M. *Acc. Chem. Res.* **1997**, *30*, 338–345; (b) Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035–1042.
11. *Typical procedure:* A solution of sulfone **10a** (50 mg, 0.188 mmol, 1.0 equiv) and 18-crown-6 (99.4 mg, 0.376 mmol, 2.0 equiv) in THF (2 mL, 0.1 M) was cooled down to −78 °C and KHMDS (451 μL, 0.5 M solution in toluene, 1.2 mmol, 1.2 equiv) was added dropwise within 10 s. After additional 30 s, aldehyde (73 mg, 0.21 mmol, 1.1 equiv) in THF (500 μL) was added. The resulting mixture was stirred at −78 °C for 30 min before saturated aqueous NH_4Cl (10 mL) was added. The resulting phases were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (P.E./EtOAc = 100:0→20:1) yielding 54.4 mg (82%) of colorless oil ((*E*/*Z*) = >50:1).