Asymmetric Catalysis

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Asymmetric Organocatalysis with Sulfones

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asymmetry · desulfonylation · diversity-oriented synthesis · organocatalysis · sulfones

Asymmetric organocatalysis has become a powerful tool for the synthesis of optically active compounds. Whereas early research mainly focused on combining simple reagents as a proof-of-concept for asymmetric organocatalysis, recent investigations are directed towards extending the concept to more target- and diversity-oriented synthesis. As a result of the many transformation possibilities and their ability to generate both nucleophilic and electrophilic reaction partners, sulfones have become especially important substrates in the field of organocatalysis.

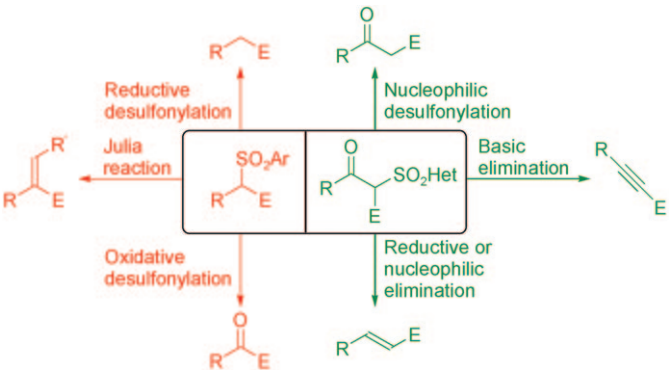
1. Introduction

Since the turn of the millennium, the field of asymmetric organocatalysis has been the focus of immense research and development.[1] It has evolved from its infancy through the "gold rush" and has emerged as a powerful tool for asymmetric synthesis, which has become increasingly suitable in a range of synthetic disciplines such as target- and diversity-oriented synthesis. Important for this development has been the application of a variety of functional groups, such as sulfones, as reaction partners,[2] which have greatly contributed to the overall synthetic applicability of asymmetric organocatalysis. The strong inductive ability of the sulfone group makes it ideal for various types of organocatalyzed reactions, and the many possible transformations of the sulfone functionality make the subsequent intermediates suitable for the generation of a range of important products which are otherwise difficult to obtain.

In the field of organocatalysis, aryl sulfones have usually been employed as electron-withdrawing groups to increase the electrophilicity or nucleophilicity of a parent reagent. Subsequent to the organocatalytic step, the sulfone functionality has traditionally been removed by various desulfonylation[3] methods, giving rise to a wide range of enantiomerically enriched building blocks (Scheme 1, left; example with nucleophilic sulfone).

More recent developments have demonstrated the ability of β-carbonyl heteroaryl sulfones to be straightforwardly transformed into alkynyl, alkenyl, and carbonyl functionalities leading to products otherwise difficult to obtain by enantioselective organocatalytic reactions (Scheme 1, right). Therefore, after the addition to an electrophile (E), new bonds between either sp–sp^3, sp^2–sp^3, or sp^3–sp^3 centers can be formed.

Considering the many newly developed transformation modes described in Scheme 1, asymmetric organocatalysis employing sulfone-containing reagents should be regarded as a contribution to an emerging area of stereoselective organocatalytic diversity-oriented synthesis.[4] Herein we emphasize the importance sulfones have had on the development of organocatalysis, as well as summarize the recent developments in sulfone chemistry.



Scheme 1. General transformation possibilities of aryl sulfones (left) and β-carbonyl heteroaryl sulfones (right); E = electrophile; Het = heteroaryl.

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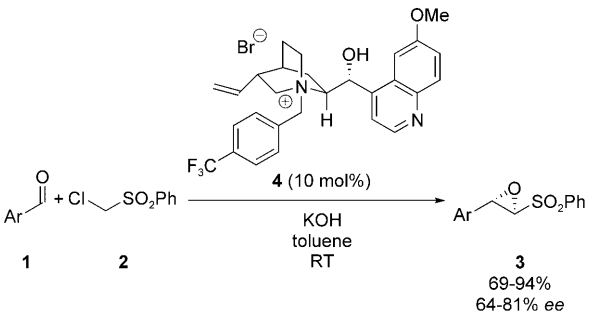
2. Target Products Containing Sulfones at a Stereogenic Center

In addition to being a very versatile donor of various functionalities and moieties, the sulfone functionality itself is gaining an increasing importance in synthetic chemistry[2] with potential in, for example, synthesizing peptide-based inhibitors.[5]

The use of a sulfone-containing reaction partner in asymmetric organocatalysis was first shown in 1998, when Arai, Ishida, and Shioiri reported the phase-transfer-catalyzed synthesis of *trans*-α,β-epoxysulfones **3** using a Darzen approach.[6a] α-Chlorophenylsulfone (**2**) was shown to undergo addition to the aromatic aldehydes **1** and the resulting products were, after the intramolecular cyclization, obtained in good yields with enantioselectivities in the range of 64–81% *ee* using catalyst **4** (Scheme 2).

This approach was later extended by the same group and it was found that the enantiopurities of products **3** could be significantly improved by the addition of 10 mol% $Sn(OTf)_2$.[6b] In 2007, Jew, Jeong, and co-workers developed a similar, but improved catalytic system for this procedure, giving rise to **3** in 95% yield and 97% *ee*.[6c] Recently, it was shown that similar products can be obtained in an organocatalytic manner by the asymmetric epoxidation of α,β-unsaturated sulfones.[7]



Scheme 2.

In 2004, the reaction between phenylsulfonylacetophenone (**5**) and aryl-substituted α,β-unsaturated ketones **6**, providing the domino Michael/aldol product **7**, was described (Scheme 3).[8] The reaction was conducted using 10 mol% of the phenylalanine-derived imidazoline catalyst **8** and led to highly stereoenriched products. An important feature was that the products were isolated by a simple filtration procedure, thereby avoiding tedious chromatographic processes. Unfortunately, changing the substitution pattern in **5** from phenyl- to alkyl-substituted β-keto sulfones led to a severe reduction in product formation (< 5%).

Another example of an enantioselective organocatalytic approach towards sulfone-containing products was shown by Cid, García Ruano, and co-workers, who demonstrated the synthesis of α,α-disubstituted cyanosulfones **12** and **13**

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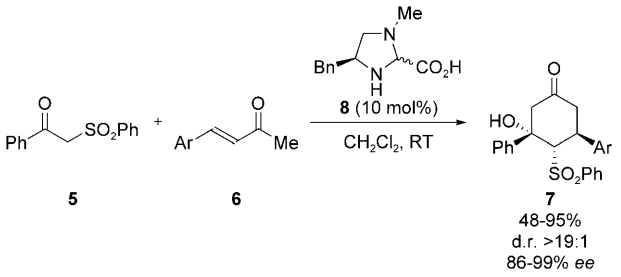
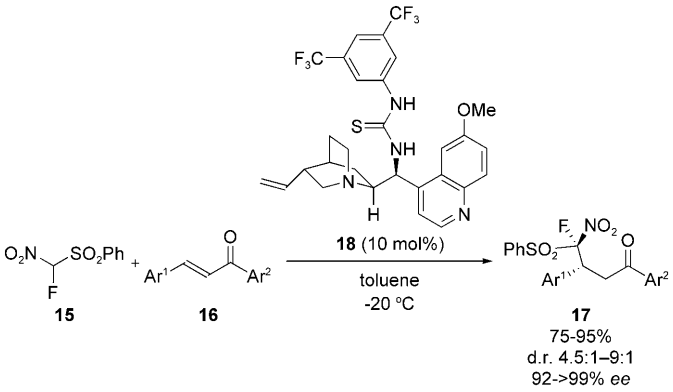
Karl Anker Jørgensen *received his PhD from Aarhus University in 1984. He was post-doc with Professor Roald Hoffmann, Cornell University, 1985. In 1985 Karl Anker Jørgensen became an Assistant Professor at Aarhus University and in 1992 he moved up the ranks to Professor. His research interests are the development, understanding, and application of asymmetric catalysis.*



Scheme 3.



Scheme 5.

(Scheme 4).[9] Performing the reaction between α-aryl-substituted cyanosulfones **9** and either vinyl ketones **10** or cyclic α,β-unsaturated ketones **11**, with catalytic amounts of cinchonine derivative **14**, led to **12** or **13**, respectively, in good to excellent yields (of the major diastereomer of **13**) and reasonable enantioselectivity. It was demonstrated that a catalyst loading as low as 1 mol% could be used without erosion of the enantioselectivity; unfortunately, employing the corresponding pseudoenantiomer of **14** resulted in a significant drop in the enantioselectivity (36% versus 70% *ee*). Finally, analogues of **12** and **13** were crystallized to give enantiopure compounds, which greatly contributed to the synthetic applicability of these reactions.

Prakash and Olah have reported the use of α-fluoro-α-nitro(phenylsulfonyl)methane (FNSM; **15**) as a reaction partner with **16** in the presence of catalytic amounts of the thiourea-derived quinine **18**, which led to the highly valued enantioenriched fluorine-containing products **17** (Scheme 5).[10,11] Yields ranging from 75–95% and excellent stereoselectivity (up to 99% *ee*) were achieved.

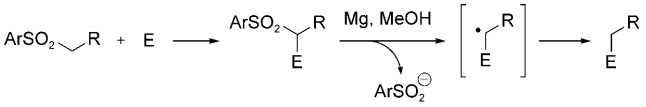
3. Sulfones as Activators of Nucleophiles

Within the last few years, the sulfone moiety has emerged as a very powerful activator for a range of otherwise inactive nucleophilic units. Nowadays, two major classes of sulfones exist: The aryl sulfones[2c] are in particular used as carriers of alkyl units. On the contrary, the β-carbonyl heteroaryl sulfones are reported to afford alkynes, alkenes, and carbonyl compounds. Furthermore, subsequent rearrangements of the organocatalyzed adducts have provided important desulfonylated products. As the mechanisms of the various desulfonylation procedures of these two classes are very different, and because each class has distinct advantages over the other, they are divided into two subsections.

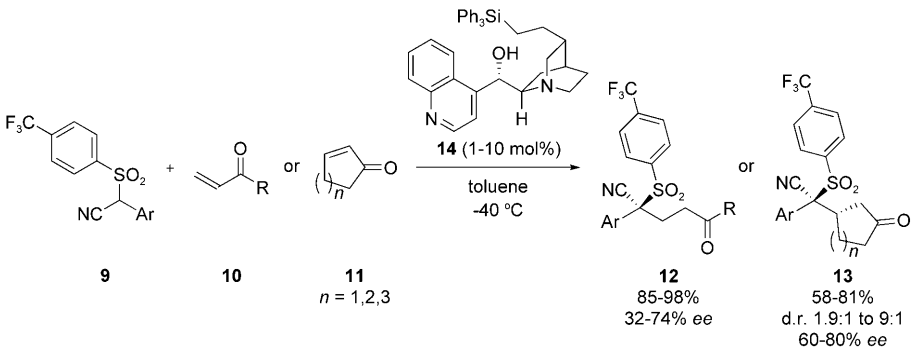
3.1. Aryl Sulfones

Aryl sulfones have mainly been used as donors of methyl or methylene units. A nucleophilic aryl sulfone provides an alkyl unit by means of an addition to an electrophile (E) and subsequent reductive desulfonylation. As depicted in Scheme 6, the latter reaction proceeds by a radical mechanism in which a phenylsulfinate is cleaved from the adduct. Protection of a carbonyl functionality present in the substrate may be necessary to avoid Barbier-type side reactions.[12]

In 2009, two publications on the enantioselective organocatalyzed addition of bis(phenylsulfonyl)methane (BSM; **19**) to α,β-unsaturated aldehydes **20** have been reported (Scheme 7). García Ruano, Marcos, and Alemán showed that



Scheme 6. General mechanism of the reductive desulfonylation of aryl sulfones.

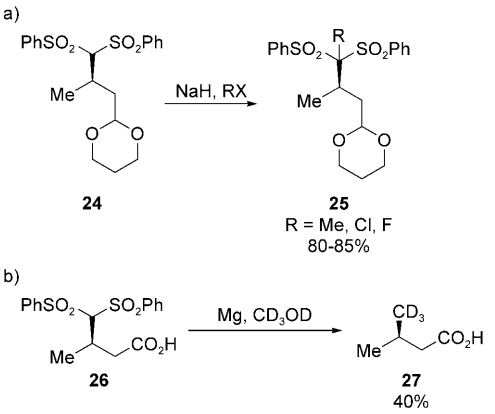


Scheme 4.

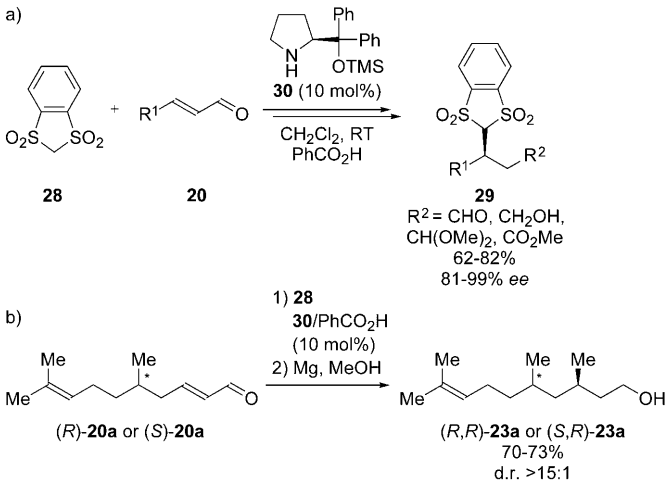
20 mol% of diarylprolinol silylether **22** catalyzes the reaction with excellent stereoselectivitiy of 96% *ee*.[13] LiOAc proved to be essential for the reaction to proceed, and both enantiomers of the product were available by use of either **22** or *ent*-**22**. Only alkyl-based aldehydes **20** were reported to undergo conversion under these reaction conditions. Performing the reductive desulfonylation procedure on **21** allowed formation of the highly valuable compounds **23**, many of which are important building blocks for targets such as pheromones, terpenoids, and a number of biologically active compounds.[14]

Moyano, Rios, and co-workers also reported the addition of **19** to alkyl-substituted α,β-unsaturated aldehydes **20** by using a similar catalytic procedure.[15] In contrast to the publication of García Ruano, Marcos, and Alemán, these reactions proceed without the addition of an external base, and the subsequent conversion of the carbonyl moiety into acid, ester, and amide functionalities was also shown. As outlined in Scheme 8a, the anion-stabilizing nature of the bis(sulfone) moiety in **24** was additionally exploited to access the additionally substituted products **25**. The synthesis of deuterium-labeled **27** by reductive desulfonylation of **26** is interesting as deuterium-containing compounds are widely used in studies of metabolism as well as in specific drugs (Scheme 8b).[16]

Expanding the scope of these alkylation reactions, Palomo and co-workers applied the cyclic bis(sulfone) **28** to react with both alkyl- and aryl-based α,β-unsaturated aldehydes **20** catalyzed by diphenylprolinol silylether **30** to afford the adduct **29** in moderate to high yields with high stereoselectivities (Scheme 9a).[17] The ability of **28** to react with both alkyl- and aryl-substituted α,β-unsaturated aldehydes was suggested to result from the higher nucleophilicity of the cyclic **28** compared to the acyclic **19**. Interestingly, the highly diastereoselective methylation of both enantiomers of the citronellal derivatives **20a** gave rise to **23a**, containing the 1,3-dimethyl array commonly found in deoxygenated polyketide-type natural products (Scheme 9b).[18] In addition, a range of alkylations of the activated methine unit in adduct **29** led to products analogous to **25**, and subsequent desulfonylations were shown to provide various β-alkyl-substituted alcohols and aldehydes. In the desulfonylation step of **29** it was reported that a chlorine substituent ($R^1 = 4\text{-}ClC_6H_4$) was tolerated, whereas a nitro group was not. Finally, a direct reductive desulfonylation on the aldehyde version of **29** (R^2 = CHO) was found feasible, leading to β-alkylated alcohols without any Barbier-type products. Hence, a concomitant reduction of the aldehyde unit into the corresponding alcohol was observed.

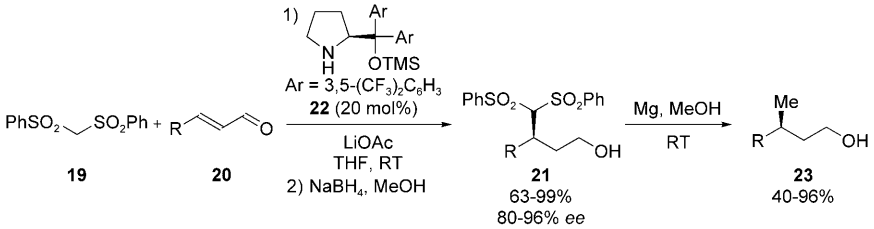


Scheme 8.

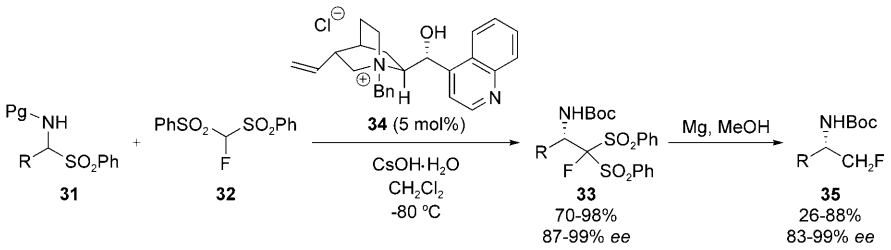


Scheme 9. R^1 = aryl or alkyl.

After nitrogen, fluorine is the second most widespread heteroelement in life science oriented research.[19] Therefore, asymmetric organocatalytic incorporation of fluorine-containing moieties is highly interesting. In an approach towards such compounds, Shibata, Toru, and co-workers showed in 2007 that α-fluorobis(phenylsulfonyl)methane (FBSM; **32**) reacts with alkyl and aryl N-Boc-protected imines, generated in situ from α-amido sulfones **31**,[20,21] leading to adduct **33** (Scheme 10). The reaction was conducted under phase-transfer conditions using 5 mol% of **34** as the catalyst. Subsequently, **33** was submitted to reductive desulfonylation



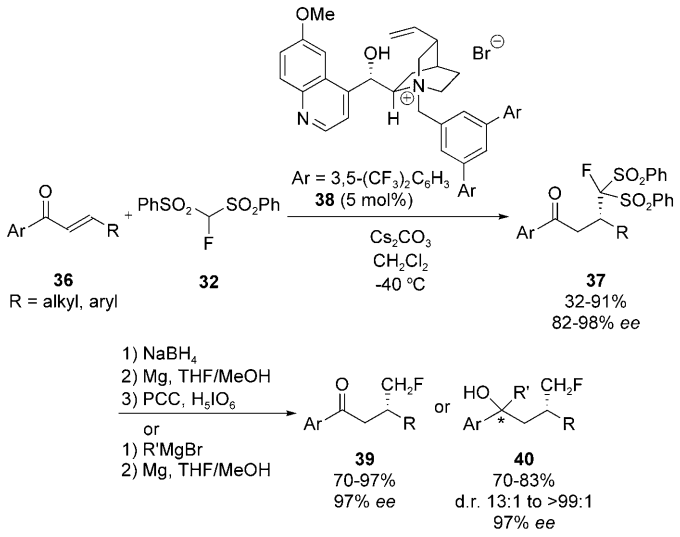
Scheme 7. TMS = trimethylsilyl, R = alkyl.



Scheme 10. Boc = *tert*-butoxycarbonyl, Bn = benzyl, R = aryl or alkyl, Pg = Boc.

conditions, providing the fluoromethylated products **35** in low to high yields without any serious erosion of the enantiopurities. Notably, only the adduct **33** derived from the sulfone **31**, where R = *tert*-butyl and Pg = Boc, gave a disappointing yield of 26% in these desulfonylation reactions, and all other examples yielded the products **35** in greater than 75% yield starting from **33**.

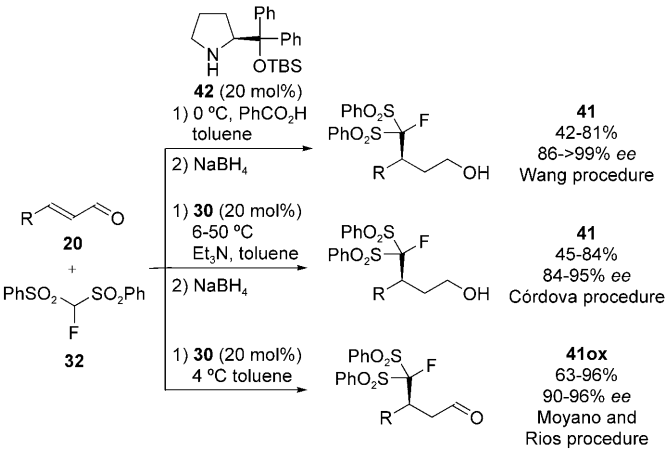
After this first report on organocatalytic enantioselective fluoromethylation, the same group extended the methodology to include α,β-unsaturated ketones **36** (Scheme 11) in 2008.[22] Using phase-transfer catalyst **38**, the corresponding



Scheme 11. PCC = pyridinium chlorochromate.

adducts **37** were formed in poor to very high yields with good to excellent enantiomeric excesses. These adducts could be reduced to the corresponding alcohol, subjected to desulfonylation, and then reoxidized to give products **39**. Alternatively, addition of a Grignard reagent to the carbonyl moiety of **37** and subsequent desulfonylation could be conducted with excellent diastereoselectivity to provide **40**. Both the reduction and Grignard reactions occurred without any loss of enantiopurity and in acceptable to good yields. An alternative organocatalytic procedure for the preparation of products similar to **37** and **39** using a chiral primary amine catalyst was reported by Kim and co-workers in 2009.[23]

In 2009, the groups of Wang, Córdova, and Moyano and Rios independently reported the fluoromethylation of α,β-unsaturated aldehydes **20** using **32** as the nucleophile (Scheme 12).[24] Although differing in catalytic conditions,

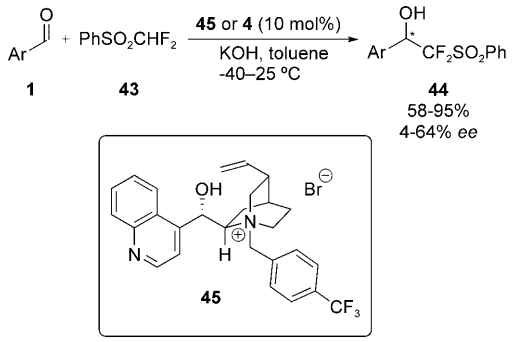


Scheme 12. TBS = *tert*-butyldimethylsilyl, R = aryl or alkyl.

all procedures form the products **41** in moderate to high yields with high to excellent enantioselectivities. Both alkyl and aromatic substituents on the α,β-unsaturated aldehydes **20** were tolerated, and subsequent removal of the sulfones, generating the fluoromethylated products in up to 96% yield from **41**, were shown for some examples in each publication.

Hu and co-workers showed the enantioselective organocatalyzed 1,2-addition of α,α-difluoro(phenylsulfonyl)methane (**43**) to aromatic aldehydes **1** under phase-transfer conditions (Scheme 13).[25] Although the enantioselectivities did not exceed 64% *ee*, this procedure constitutes the only reported organocatalytic asymmetric 1,2-addition of sulfone nucleophiles to carbonyl compounds to date. In addition, it is the only described organocatalyzed asymmetric difluoromethylation process employing sulfone nucleophiles. Subsequent removal of the sulfone moiety was shown for one example (Ar = Ph), giving the pure diflouromethylated compound in 93% yield from **44** without any erosion of optical purity. To obtain the highest enantiomeric excesses for either enantiomer, different catalysts, either **45** or **4**, were found to be optimal.

The synthetic versatility of the aryl sulfone moiety was additionally explored by Bernardi, Ricci, and co-workers in



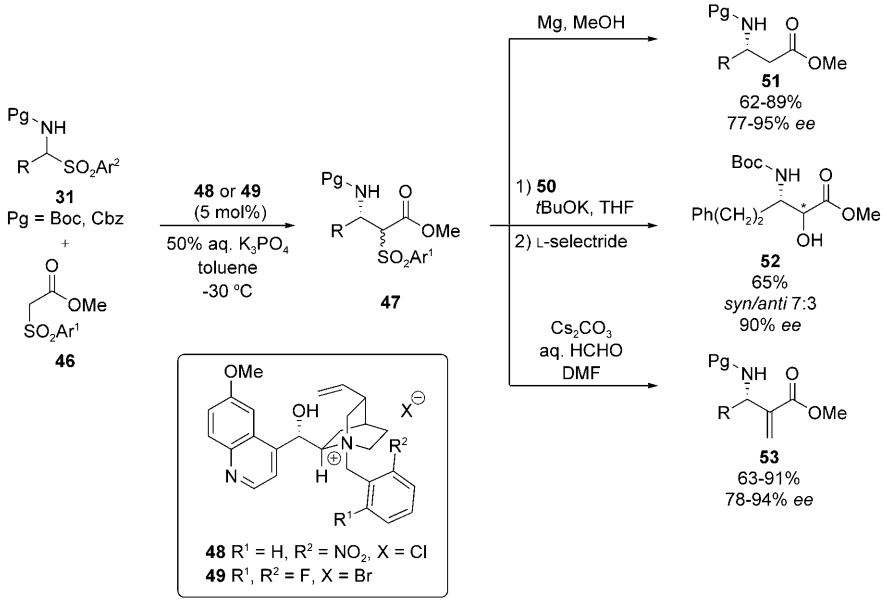
Scheme 13.

2009 (Scheme 14).[26] Adding arylsulfonylacetates **46** to in situ formed imines under phase-tranfer conditions gave rise to intermediates **47**. No yields of isolated **47** were reported, but three types of post-organocatalytic transformations, utilizing the various transformation possibilities of the aryl sulfone, were described. In one example, traditional reductive desulfonylation resulted in **51** in moderate to high yields with moderate to excellent stereoselectivities. As expected, a bromine substituent in **47** ($R = 2\text{-}BrC_6H_4$) did not survive this magnesium treatment. Performing an oxidative desulfonylation using phenylsulfonyloxaziridine **50** and subsequent diastereoselective reduction of the ketone unit with L-selectride afforded **52** in moderate yield with low diastereoselectivity; however, high enantioselectivity was observed. Finally, when using the 4-nitrophenylsulfonylacetate nucleophile **46** ($Ar^1 = 4\text{-}NO_2C_6H_4$) a Julia–Kocienski[27] reaction on the corresponding **47** provided the N-carbamate-protected aza-Morita-Baylis–Hillman product **53** in moderate to excellent yields and enantiomeric excesses.

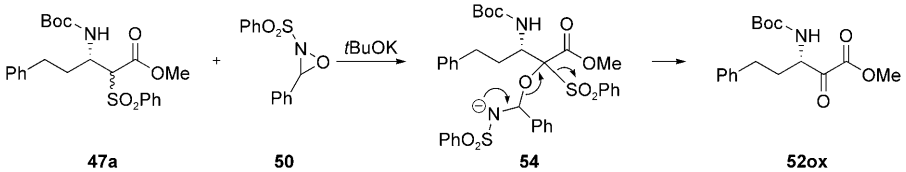
The mechanism for the oxidative desulfonylation affording oxidized **52** is proposed in Scheme 15. In contrast to the reductive desulfonylation, this reaction does not proceed through a radical mechanism. By taking advantage of the electron-withdrawing sulfone, the adduct **47a** adds to the electrophilic oxygen atom of oxaziridine **50** to form intermediate **54**. Collapse of **54** affords the product **52ox**.

3.2. Heteroaryl Sulfones

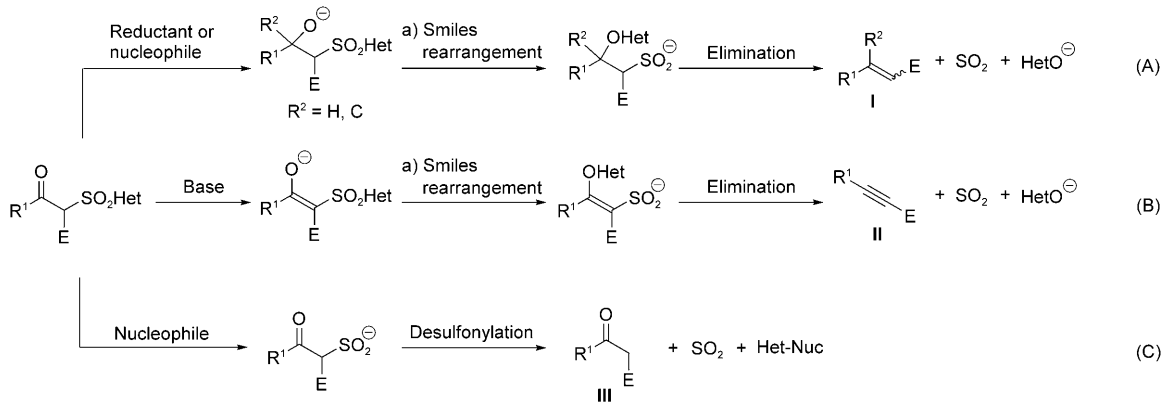
While the aryl sulfone adducts desulfonylate by an elimination of the aryl sulfone as one unit, recent developments have shown that desulfonylation of the heteroaryl sulfones can proceed by an initial C–S bond cleavage between the heteroaryl and sulfone moieties. Although this might appear as a mere mechanistic curiosity, it provides the synthetic chemist with a range of additional transformation modes. This mode has been used in connection with β-carbonyl heteroaryl sulfones as nucleophiles. For clarity, Scheme 16 shows the general reaction mechanisms for the



Scheme 14. Cbz = benzyloxycarbonyl, DMF = *N*,*N*-dimethylformamide.



Scheme 15. Mechanism for the oxidative desulfonylation of **47a**.

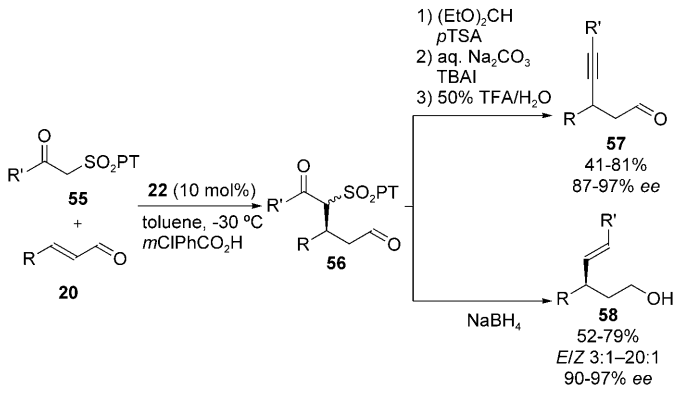


Scheme 16.

developed transformations which have been employed in connection with asymmetric organocatalysis, clearly emphasizing the difference between these reactions and the aryl sulfone based desulfonylation reactions.

The reactions A and B in Scheme 16 both rely on the generation of an intermediate alkoxide, which undergoes a Smiles rearrangement,[28] and subsequent elimination to give the corresponding alkene **I** or alkyne **II**. In contrast, the mechanism of reaction C relies on an initial S_NAr reaction of an organic nucleophile on the heteroaryl sulfone moiety, eventually leading to the desulfonylated product **III**.

The first application of β-keto heteroaryl sulfones was recently reported by our group.[29] The addition of β-keto phenyltetrazole sulfones **55** to α,β-unsaturated aldehydes **20** catalyzed by diarylprolinol silylether **22** gave rise to the key intermediate **56**, which was then transformed into highly valuable alkynes **57** and alkenes **58** (Scheme 17). These types of products are privileged classes of stereoenriched compounds having wide applications in various fields of chemistry, and are precursors for a broad range of biologically active compounds. Both **57** and **58** were obtained in moderate to high yields with excellent stereoselectivities. Only the alkyl-substituted **20** proved to be reactive in the organocatalyzed addition step. For the alkyne formation, in situ protection of the aldehyde unit in adduct **56** was found to be necessary to obtain yields higher than approximately 30%. Importantly, this procedure was the first example of the enantioselective formation of β-alkyne-substituted aldehydes.[30]



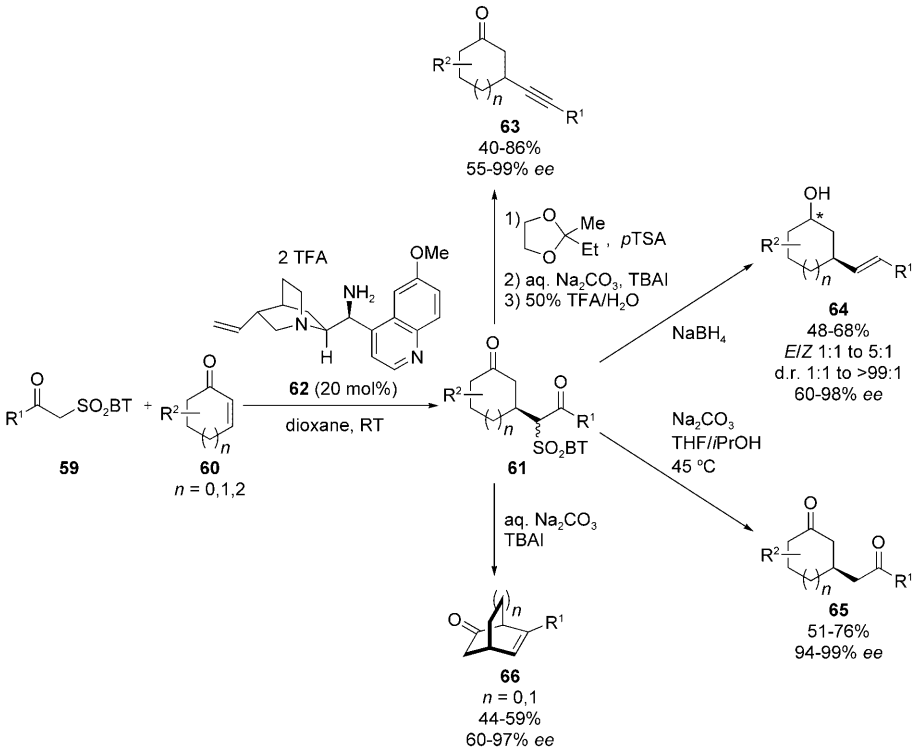
Scheme 17. PT = phenyltetrazole, *p*TSA = *para*-toluenesulfonic acid, TBAI = tetra-*n*-butylammonium iodide, TFA = trifluoroacetic acid, R = alkyl.

After this initial study, our group reported the reaction between β-keto benzothiazole sulfones **59** and cyclic α,β-unsaturated ketones **60** catalyzed by primary amine derived quinine **62** to provide the key intermediate **61** (Scheme 18).[31] Subsequently, by using similar procedures as described above, intermediates **61** were transformed into alkynes **63** and alkenes **64** in moderate to high yields with up to excellent stereoselectivities. Furthermore, 1,5-diketo products **65** were also obtained in moderate to good yields and excellent enantioselecty by an organomediated desulfonylation of **61**. In this context, it was shown that the magnesium-reactive substituents, such as bromine, were tolerated under these desulfonylation conditions. Finally, an intramolecular aldol reaction and subsequent Smiles rearrangement and elimination led to bicyclic products **66** in moderate yields with up to excellent enantioselectivities.[32]

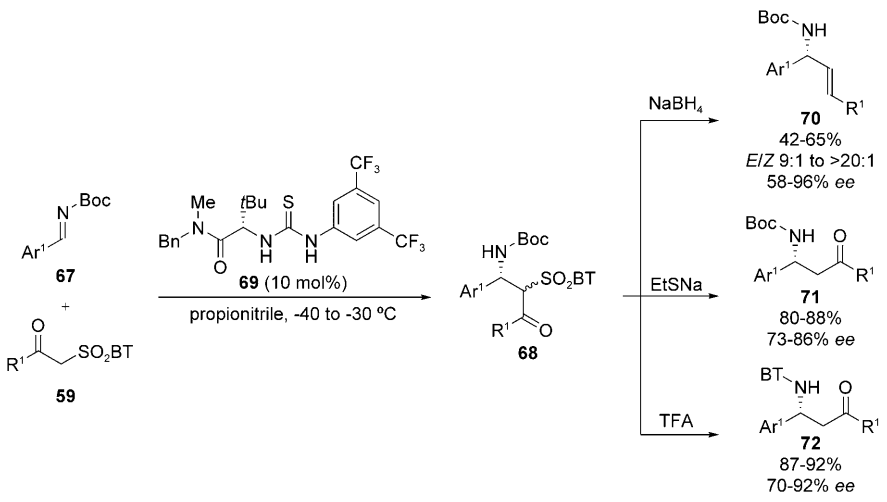
Nucleophiles **59** were also shown to undergo addition to N-Boc-protected imines **67** catalyzed by thiourea **69** leading to the adduct **68** (Scheme 19).[33] Reduction of **68** gave rise to allylic amine **70** in moderate yields and moderate to excellent stereoselectivities. The synthesis of **70** comprises the first organocatalytic method for making allylic amines in the absence of a conjugated electron-withdrawing group. Sodium ethanethiolate promoted desulfonylation provided β-amino ketones **71** in high yields and slightly diminished enantioselectivities. Interestingly, the TFA-promoted removal of the N-Boc group allowed a nitrogen-based Smiles rearrangement, which led to products **72**, containing the highly bioactive benzothiazole group,[33] in high yields with moderate to excellent enantiopurities.

4. Sulfones as Activators of Electrophiles

The electron-withdrawing ability of the sulfone moiety defines α,β-unsaturated aryl sulfones as excellent Michael acceptors. Therefore, the application of vinyl sulfones as electrophilic reaction partners in organocatalytic reactions



Scheme 18. BT = benzothiazole.

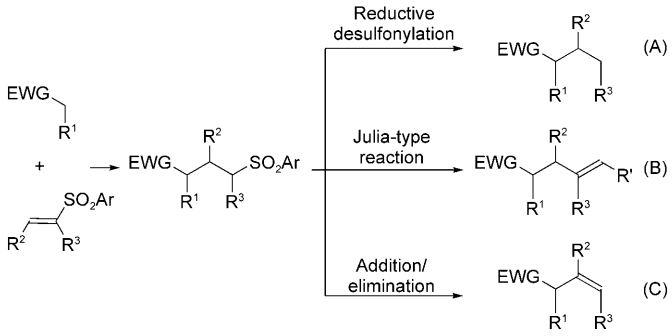


Scheme 19. R^1 = aryl.

has gained broad synthetic interest during the last years. Mostly, the sulfone group has been subsequently removed under reductive conditions and therefore served to activate the double bond towards nucleophilic attack (Scheme 20, A). Nevertheless, a few examples have been published in which either Julia-type reactions were performed (Scheme 20, B) or the sulfone functionality acted as a leaving group in the organocatalytic step (addition/elimination; Scheme 20, C), resulting, in both cases, in the formation of alkene-containing products. An overview of recent progress in the organocatalytic conjugate addition of various nucleophiles to α,β-unsaturated aryl sulfones is outlined in this section, and categorized based on the transformation of the sulfone moiety, which is primarily performed after the organocatalytic step.

4.1. Reductive Desulfonylation

The first organocatalytic conjugate addition to vinyl bis(sulfone) **74** was reported in 2005 by Mossé and Alexakis (Scheme 21).[34] By using the isopropyl-substituted bipyrrolidine (*i*PBP) catalyst **77**, the highest enantioselectivity (up to 80% *ee*) was achieved, although a catalyst loading of

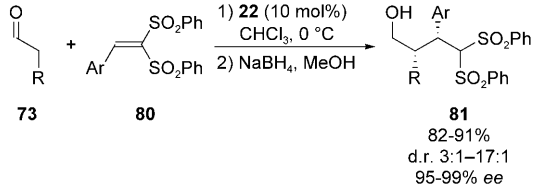


Scheme 20. Possible applications of the sulfone moiety in organic synthesis. EWG = electron-withdrawing group.

25 mol% was necessary to obtain full conversion. The formation of the by-product **76**, arising from 1,4-addition of the in situ generated bis(phenylsulfonyl)methane anion to **74**, could only be suppressed by using 10 equivalents of aldehyde **73**. With this general procedure, branched and unbranched aldehydes were reacted with sulfone **74** resulting in good yields, but only in a few cases with good enantioselectivity. The reaction seemed to be highly substrate dependent and although the first example of conjugate addition to vinylic bis(sulfone) had been achieved, significant challenges remained to be solved. Interestingly, an improved method for the synthesis of **75** was later presented by the same group.[12] By application of diphenylprolinol silylether **30** as the catalyst, the enantioselectivity could be improved to 98% *ee*, and at the same time allow a lowering of the amounts of the aldehyde (2 equiv) and catalyst (1 mol%) used. Furthermore, the formation of the by-product **76** was not observed.

The selective removal of only one aryl sulfone group (**78**) was successful by treatment of the reduced and protected version of **75a** with samarium diiodide (Scheme 22).[12] As mentioned in Section 3.1, an unprotected aldehyde can lead to a Barbier-type product, as shown by subjection of **75a** to the same samarium diiodide conditions. The reductive cyclization process resulted in cyclobutanol **79** as a single diastereoisomer albeit with lower enantiopurity.

Substituted α,β-unsaturated aryl sulfones **80** were successfully applied by Zhu and Lu, giving access to the *syn*-configured alcohols **81** with excellent enantioselectivities and high diastereoselectivities (Scheme 23).[35] Aromatic groups

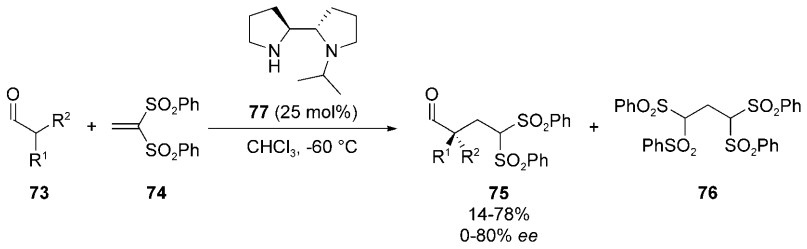


Scheme 23.

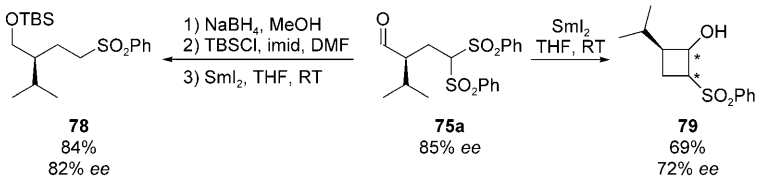
having electron-donating or electron-neutral substituents were well-tolerated; however, the preparation of electron-poor aryl-substituted sulfones failed. Furthermore, it was also shown that the application of diarylprolinol silylether **22**, as the catalyst in the addition reaction to unsubstituted vinylic sulfone **74**, led to additional improvement in both yield and enantioselectivity compared to those obtained by employing the catalyst **30**.

The aryl sulfone groups could be cleaved without loss of enantioselectivity, giving access to useful chiral building blocks. For example, in addition to the reduction of **75b** into the corresponding alcohol **82**, oxidation into the carboxylic acid **83** or reductive amination to provide **84** could also be carried out, prior to subjection to Mg in MeOH (Scheme 24).[35]

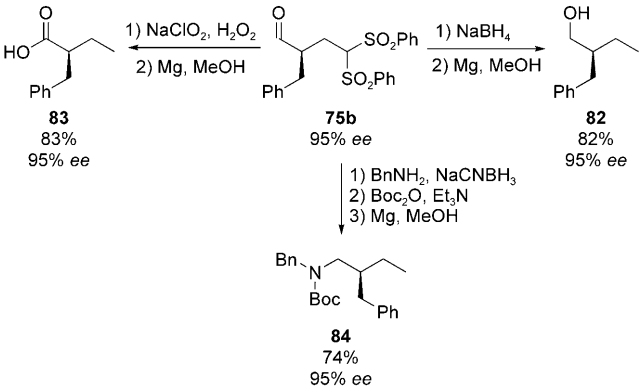
The first conjugate addition of cyclic ketones **85** to vinyl sulfone **74** was reported by Lu and co-workers, utilizing the cinchonidine-derived catalyst **87** (Scheme 25).[36] Various cyclic ketones could be applied, affording the products **86** with excellent enantioselectivities. However, linear ketones proved to be unsuitable substrates for this Michael reaction.



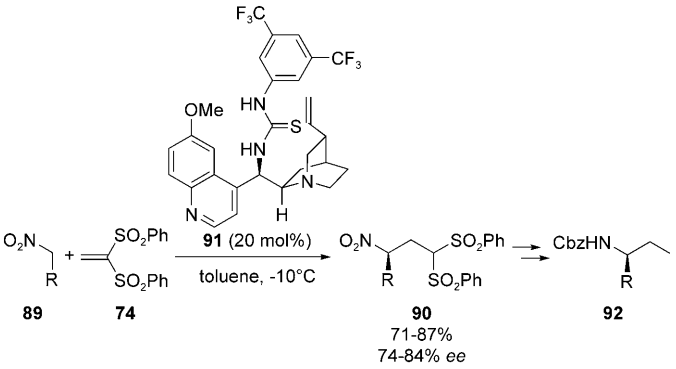
Scheme 21.



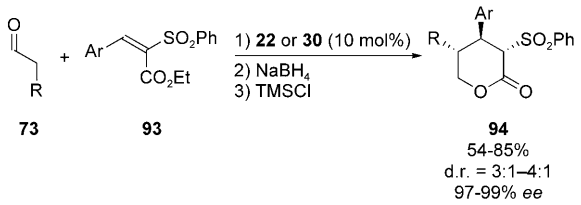
Scheme 22.



Scheme 24.



Scheme 26.



Scheme 27.

To emphasize the synthetic utility of the obtained enantioenriched α-substituted ketones **86**, a desulfonylation was carried out in combination with carbonyl group transformations, giving rise to (*S*,*S*)-sodium cyclamate (**88**).

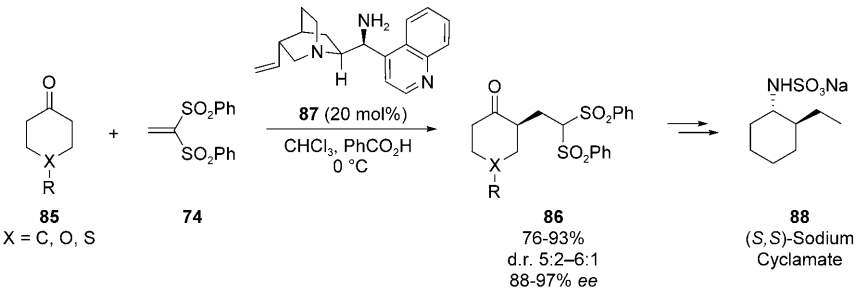
More recently, the conjugate addition of aliphatic nitroalkanes **89** to **74** was accomplished by the same group.[37] The application of the quinidine-derived thiourea catalyst **91** resulted in high yields and good enantioselective formation of **90** (Scheme 26). Reduction of the nitro functionality, in combination with desulfonylation, gave access to optically active amines **92**.

Palomo and co-workers recently studied the partial substitution of the bis(sulfone) **74** against other activating groups such as nitriles or esters.[38] In this context, it was shown that aryl-substituted α-ethoxycarbonyl vinyl sulfones **93** could successfully be reacted with the different aldehydes **73**, whereas the corresponding aryl-substituted α,β-unsaturated malonates failed under the same reaction conditions (Scheme 27). The obtained Michael adducts were reduced in situ and in a separately performed step converted into the corresponding δ-lactones **94**. In all cases, excellent enantioselectivity, together with reasonable diastereoselectivity could be achieved.

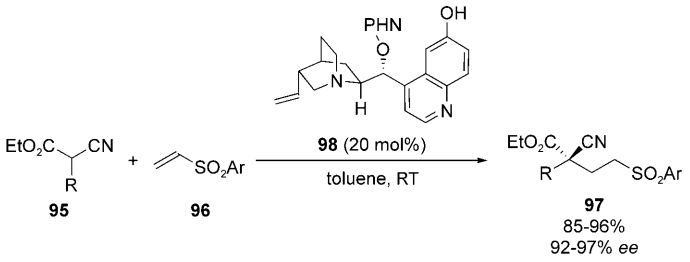
4.2. Julia-Type Reactions

During the course of their studies for the creation of all-carbon quaternary stereocenters, Deng and co-workers[39] synthesized α,α-disubstituted amino acid derivatives, using a Julia reaction as the key step.[39a] In this context, α,α-disubstituted Michael donors **95** were initially reacted with different α,β-unsaturated aryl sulfones **96** (Scheme 28). Depending on the nature of the R substituent in **95**, different aryl sulfones should be applied to obtain full conversion. Whereas for R = aryl the normally used phenyl sulfone afforded the corresponding products **97** in high yields and enantioselectivities, the electrophilicity of the sulfone had to be increased for R = alkyl. By using 3,5-bis(trifluoromethyl)-phenylsulfone, aliphatic-substituted cyano acetates reacted smoothly, furnishing the addition products in good yields. Both enantiomers were accessible with similar enantioselectivities using **98** and its quasienantiomer. Similar reactions were also later studied by Chen and co-workers, using thioureas as the catalytic system.[40] However, no significant improvements were achieved.

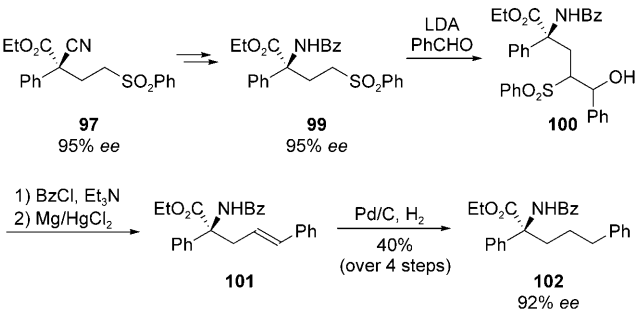
After transformation of the cyano group in **97** into the benzoate protected amine **99**, the Julia reaction was carried out, which involved the addition to benzaldehyde to give **100**, then benzoylation and reductive elimination to give **101** (Scheme 29). Final hydrogenation of the formed alkene



Scheme 25.



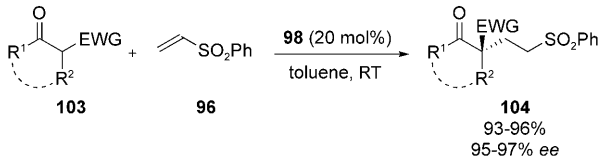
Scheme 28. PHN = phenanthryl.



Scheme 29. Bz = benzoyl, LDA = lithium diisopropylamine.

moiety gave rise to the amino acid derivative **102**, which has not previously been accessible by asymmetric catalysis.

The concept of creating all-carbon quaternary stereocenters was recently extended by the same group to the addition of the cyclic β-keto compounds **103** to phenyl sulfone **96** (Scheme 30).[39b] Although, linear β-ketoesters were not

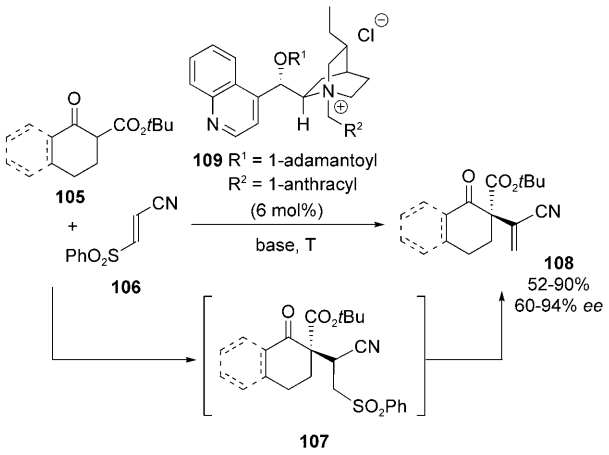


Scheme 30.

applicable, the yields and enantioselectivity obtained by utilization of cyclic derivatives were consistently excellent.

4.3. The Sulfone Moiety as Leaving Group

A different concept for the utilization of the sulfone group was presented in 2007 by our group.[41] In the course of performing *anti*-Michael reactions, the sulfone functionality was employed both as a directing group in the organocatalytic step and as leaving group afterwards, furnishing optically active Morita-Baylis–Hillman like adducts **108** (Scheme 31). Different cyclic β-ketoesters **105** were reacted under phase-transfer conditions with the electrophile **106**, giving direct access to the *anti*-Michael product **108** without isolation of the intermediate **107**. Depending on the structure of nucleophile **105**, different bases and reaction temperatures were used to obtain optimal yields and enantioselectivity.



Scheme 31.

5. Summary

Recently, employing sulfones in asymmetric organocatalysis has emerged as a powerful tool for the stereoselective incorporation of various otherwise inactive units in a wide range of compounds. These units comprise moieties such as alkynes, alkenes, alkanes, and carbonyl functionalities. The described reactions show the versatility of sulfone reactants in their ability to react with different electrophiles and nucleophiles under a variety of stereoselective organocatalytic conditions. Furthermore, the reactions show that the sulfone moiety, while having the distinct advantage of being converted into a variety of different functionalities, is also able to survive reaction conditions used to transform other functionalities within the given adducts, thereby greatly enhancing its synthetic applicability.

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[1] For some reviews on organocatalysis, see: a) P. L. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; c) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; d) Special issue on organocatalysis, *Acc. Chem. Res.* **2004**, *37*(8); e) M. Ueda, T. Kano, K. Maruoka, *Org. Biomol. Chem.* **2009**, *7*, 2005; f) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; g) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; h) Special issue on organocatalysis, *Chem. Rev.* **2007**, *107*, 5413; i) M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904; j) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33; k) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; l) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

[2] For descriptions of sulfone chemistry, see: a) N. S. Simpkins, *Sulphones in Organic Synthesis*, Pergamon, Oxford, **1993**; b) T.

Toru, C. Bolm, *Organosulfur Chemistry in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2008**. For a review on organic chemistry based on the phenylsulfone moiety, see e.g.: c) A. El-Awa, M. N. Noshi, X. M. Jourdin, P. L. Fuchs, *Chem. Rev.* **2009**, *109*, 2315. For a review on vinylsulfones in medicinal chemistry, see: d) D. C. Meadows, J. Gervay-Hague, *Med. Res. Rev.* **2006**, *26*, 793. For synthetic applications using phenylsulfones, see: e) C. Liu, M. Li, D. Cheng, C. Yang, S. Tian, *Org. Lett.* **2009**, *11*, 2543; f) G. K. S. Prakash, S. Chacko, H. Vaghoo, N. Shao, L. Gurung, T. Mathew, G. A. Olah, *Org. Lett.* **2009**, *11*, 1127; g) C. Ni, L. Zhang, J. Hu, *J. Org. Chem.* **2009**, *74*, 3767; h) A. K. Ghosh, S. Banerjee, S. Sinha, S. B. Kang, B. Zajc, *J. Org. Chem.* **2009**, *74*, 3689; i) C. Ni, L. Zhang, J. Hu, *J. Org. Chem.* **2008**, *73*, 5699.

[3] For a review on desulfonylations, see: C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547.

[4] M. Amatore, T. D. Beeson, S. P. Brown, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 5223; *Angew. Chem. Int. Ed.* **2009**, *48*, 5121.

[5] B. Lovejoy, A. R. Welch, S. Carr, C. Luong, C. Broka, R. T. Hendricks, J. A. Campbell. K. A. M. Walker, R. Martin, H. Van Wart, M. F. Browner, *Nat. Struct. Biol.* **1999**, *6*, 217.

[6] a) S. Arai, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 8299; b) S. Arai, T. Shioiri, *Tetrahedron* **2002**, *58*, 1407; c) J. Ku, M. Yoo, H. Park, S. Jew, B. Jeong, *Tetrahedron* **2007**, *63*, 8099.

[7] a) J. Lopez-Pedrosa, M. R. Pitts, S. M. Roberts, S. Saminathan, J. Whittall, *Tetrahedron Lett.* **2004**, *45*, 5073; b) R. L. Dorow, S. A. Tymonko, *Tetrahedron Lett.* **2006**, *47*, 2493.

[8] J. Pulkkinen, P. S. Aburel, N. Halland, K. A. Jørgensen, *Adv. Synth. Catal.* **2004**, *346*, 1077.

[9] a) M. B. Cid, J. López-Cantarero, S. Duce, J. L. García Ruano, *J. Org. Chem.* **2009**, *74*, 431.

[10] G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4090.

[11] For papers regarding fluorine-containing compounds, see: a) F. Cottet, M. Marull, O. Lefebvre, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 1559; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.

[12] S. Sulzer-Mossé, A. Alexakis, J. Mareda, G. Bollot, G. Bernardinelli, Y. Filinchuk, *Chem. Eur. J.* **2009**, *15*, 3204.

[13] J. L. García Ruano, V. Marcos, J. Alemán, *Chem. Commun.* **2009**, 4435.

[14] a) S. Senda, K. Mori, *Agric. Biol. Chem.* **1983**, *47*, 795; b) B. V. Burger, W. G. B. Petersen, *J. Chem. Ecol.* **2002**, *28*, 501; c) T. Kitahara, S. Kang, *Proc. Jpn. Acad. Ser. B* **1994**, *70*, 181; d) J. Li, G. Gries, J. Bikic, K. N. Slessor, *J. Chem. Ecol.* **1993**, *19*, 2547; e) T. Suzuki, J. Ozaki, R. Sugawara, *Agric. Biol. Chem.* **1983**, *47*, 869; f) D. Raederstorff, A. Y. L. Shu, J. E. Thompson, C. Djerassi, *J. Org. Chem.* **1987**, *52*, 2337; g) K. Mori, J. Wu, *Liebigs Ann. Chem.* **1991**, *5*, 439.

[15] A. Alba, X. Companyó, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 11095.

[16] D. J. Kushner, A. Baker, T. G. Dunstall, *Can. J. Physiol. Pharmacol.* **1999**, *77*, 79.

[17] A. Landa, A. Puente, J. I. Santos, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2009**, *15*, 11954.

[18] S. Hanessian, S. Giroux, V. Mascitti, *Synthesis* **2006**, 1057.

[19] F. Cottet, M. Marull, O. Lefebvre, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 1559.

[20] For a review on the use of α-amido sulfones as precursors for imines, see: M. Petrini, *Chem. Rev.* **2005**, *105*, 3949.

[21] S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T. Toru, *J. Am. Chem. Soc.* **2007**, *129*, 6394.

[22] T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 8171; *Angew. Chem. Int. Ed.* **2008**, *47*, 8051.

[23] H. W. Moon, M. J. Cho, D. Y. Kim, *Tetrahedron Lett.* **2009**, *50*, 4896.

[24] a) S. Zhang, Y. Zhang, Y. Ji, H. Li, W. Wang, *Chem. Commun.* **2009**, 4886; b) F. Ullah, G. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahem, P. Hammar, J. Sun, A. Córdova, *Chem. Eur. J.* **2009**, *15*, 10013; c) A. Alba, X. Companyó, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 7035.

[25] C. Ni, F. Wang, J. Hu, *Beilstein J. Org. Chem.* **2008**, *4*, 21.

[26] C. Cassani, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem.* **2009**, *121*, 5804; *Angew. Chem. Int. Ed.* **2009**, *48*, 5694.

[27] a) J. B. Baudin, G. Hareau, S. A. Julia, *Tetrahedron Lett.* **1991**, *32*, 1175; b) P. R. Blakemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26. For reviews, see e.g.: c) C. Aïssa, *Eur. J. Org. Chem.* **2009**, 1831; d) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563.

[28] L. A. Warren, S. Smiles, *J. Chem. Soc.* **1930**, 1327.

[29] M. Nielsen, C. B. Jacobsen, M. W. Paixão, N. Holub, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, *131*, 10581.

[30] Following our publication, a rhodium-based asymmetric catalytic alkynylation of alkyl-substituted α,β-unsaturated aldehydes was reported: T. Nishimura, T. Sawano, T. Hayashi, *Angew. Chem.* **2009**, *121*, 8201; *Angew. Chem. Int. Ed.* **2009**, *48*, 8057.

[31] M. W. Paixão, N. Holub, C. Vilas, M. Nielsen, K. A. Jørgensen, *Angew. Chem.* **2009**, *121*, 7474; *Angew. Chem. Int. Ed.* **2009**, *48*, 7338.

[32] N. Holub, H. Jiang, M. W. Paixão, C. Tiberi, K. A. Jørgensen, *Chem. Eur. J.*, in press.

[33] C. B. Jacobsen, L. Lykke, D. Monge, M. Nielsen, L. K. Ransborg, K. A. Jørgensen, *Chem. Commun.* **2009**, 6554, and references herein.

[34] a) S. Mossé, A. Alexakis, *Org. Lett.* **2005**, *7*, 4361; see also: b) A. Quintard, A. Alexakis, *Chem. Eur. J.*, **2009**, *15*, 11 109.

[35] Q. Zhu, Y. Lu, *Org. Lett.* **2008**, *10*, 4803.

[36] Q. Zhu, L. Cheng, Y. Lu, *Chem. Commun.* **2008**, 6315.

[37] Q. Zhu, Y. Lu, *Org. Lett.* **2009**, *11*, 1721.

[38] A. Landa, M. Maestro, C. Masdeu, A. Puente, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2009**, *15*, 1562.

[39] a) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948; b) H. Li, J. Song, L. Deng, *Tetrahedron* **2009**, *65*, 3139.

[40] T. Liu, J. Long, B. Li, L. Jiang, R. Li, Y. Wu, L. Ding, Y. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097.

[41] J. Alemán, E. Reyes, B. Richter, J. Overgaard, K. A. Jørgensen, *Chem. Commun.* **2007**, 3921.