DOI: 10.1002/ejoc.201000502

Influence of the Reaction Conditions on the Evolution of the Michael Addition of β-Keto Sulfones to α,β-Unsaturated Aldehydes

José Alemán,*[a] Vanesa Marcos,[a] Leyre Marzo,[a] and José Luis García Ruano*[a]

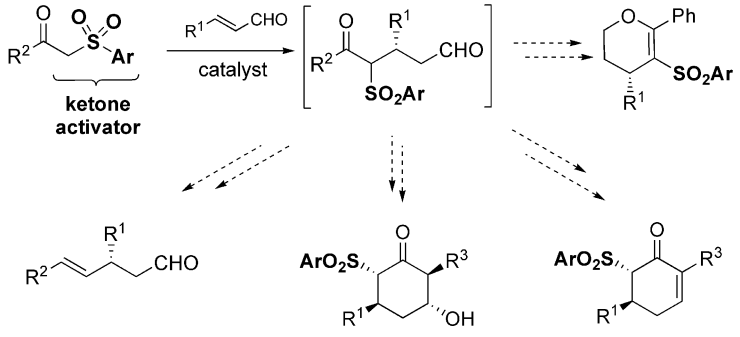
Keywords: Organocatalysis / Michael addition / Aldehydes / Keto sulfones

We have studied the influence of different reaction conditions on the conjugated addition of β-keto sulfones to α,β-unsaturated aldehydes catalyzed by silyl prolinol ethers. Small changes in the starting material and/or in the experimental protocol are able to produce significant variations in the structures of the final products. The high chemical versatility of the resulting Michael adducts make possible their use in a variety of tandem and one-pot reactions to afford polysubstituted cyclic products bearing multiple chiral centers.

Introduction

The development of cascade, tandem, and one-pot reactions[1] is currently considered a new direction in organocatalysis.[2] One-pot procedures[3] have reached this status because they lead to highly functionalized products containing multiple stereocenters in a single stroke.[3] This is the case for the organocatalytic stereoselective preparation of complex molecules with several stereocenters mediated by mechanistically diverse processes.[4] One of the most striking features of one-pot or tandem reactions is the possibility of achieving significant structural modifications in the final products by introducing small changes in the starting material and/or in the experimental protocol. In this sense there are many examples based on initial organocatalytic processes followed by different reactions (not necessarily organocatalytic processes) of the resulting products to give structurally diverse compounds,[4] one of the landmark syntheses being that of (–)-Oseltamivir by Hayashi and coworkers.[4g]

To be successful, highly versatile reagents must be involved in the first organocatalytic step. We have focused our attention on β-keto sulfones, which have recently been used in some interesting nucleophilic addition reactions[5] because they present in the same structure two versatile functions in organic chemistry (ketone and sulfone).



Scheme 1. Transformations of the primary adducts, formed by the addition of β-keto sulfones to α,β-unsaturated aldehydes, into different products by one-pot or tandem reactions.

Methylenebis(sulfones) have recently been shown to be highly efficient in the organocatalytic β-methylation of α,β-unsaturated aldehydes.[6] Thus, we reasoned that the use of β-keto sulfones in this reaction[7] would also be successful and the initial adducts could intervene in a range of one-pot or tandem reactions allowing the preparation of compounds with different structures by introducing small

[a] Departamento de Química Orgánica (C-I), Universidad Autónoma de Madrid,
Cantoblanco, 28049 Madrid, Spain
Fax: +34-91-4973966
E-mail: jose.aleman@uam.es
joseluis.garcia.ruano@uam.es

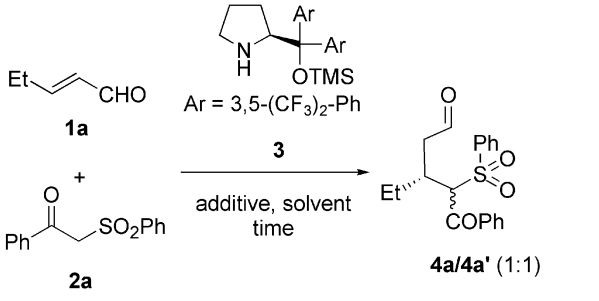
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000502.

changes in the reaction conditions. In connection with this topic, the direct organocatalytic addition of methyl phenyl ketone (pK_a = 24.7) to α,β-unsaturated aldehydes was not possible in our hands, presumably due to the low acidity of its methyl protons. The ability of the sulfonyl group to increase the pK_a of its C-α protons and the easy elimination of the sulfonyl group makes β-keto sulfones ideal as a synthetic equivalent of methyl ketones in organocatalysis (Scheme 1). In this paper we present our results on the silyl prolinol ether catalyzed addition of β-keto sulfones to α,β-unsaturated aldehydes and the multiple transformations of the primary adducts into different products by one-pot or tandem reactions (Scheme 1).

Results and Discussion

The search for the optimal conditions for the addition of β-keto sulfones to α,β-unsaturated aldehydes was performed by using 2-pentenal (**1a**) and phenylsulfonylacetophenone (**2a**) as the starting materials (Table 1). The silyl prolinol ether **3**[8] (Table 1) was used as the catalyst because it had provided the best results in the addition reactions of methylenebis-sulfones.[6] Full conversion could not be achieved with alkaline hydroxides in $CHCl_3$ or EtOH (entries 1–4), however, this problem was solved in THF (entries 5 and 6). A mixture of diastereoisomers (50:50) at the carbon flanked by the carbonyl and sulfonyl group (**4a**/**4a′**) were obtained in all cases. These epimers could not be separated because they are in equilibrium due to the high acidity of the methinic proton as occurs with β-keto esters.[8]

Table 1. Screening of phenylsulfonylacetophenone (**2a**).[a]



Entry	Additive (20 mol-%)	Solvent	Time [h]	Conv. [%]	*ee* [%][b]
1	LiOH	$HCCl_3$	72	51	n.d.[c]
2	CsOH	$HCCl_3$	72	Nr	n.d.[c]
3	KOH	$HCCl_3$	72	30	n.d.[c]
4	CsOH	EtOH	72	71	n.d.[c]
5	CsOH	THF	72	>99	84
6	LiOH	THF	72	>99	74
7	LiOAc	THF	48	>99 (91)[d]	91
8	$C_6H_5CO_2H$	THF	20	>99 (81)[d]	90

[a] Performed with **1a** (0.20 mmol), **2a** (0.4 mmol), additive (20 mol-%), and catalyst **3** (20 mol-%) in the indicated solvent (0.2 mL) at room temperature. [b] The enantiomeric excess was determined by chiral stationary phase HPLC after transformation of the epimeric mixture **4a**/**4a′** to the dihydropyran **10a** (see Table 2). [c] Not determined. [d] Isolated combined yields (**4a**/**4a′**) after flash chromatography.

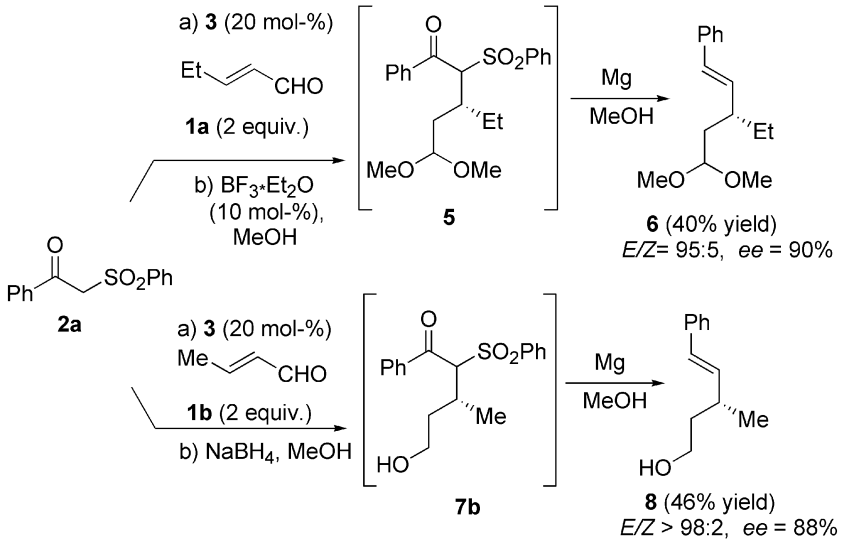
We were unable to establish the enantiomeric excess of the two epimers **4a**/**4a′** by chiral HPLC, which would have provided information about the stereoselectivity of the reaction at the β position of the aldehyde. However, their derivatization to dihydropyran **10a** did allow the determination of the enantiomeric excess (see later, Table 2). The use of weaker bases, such as LiOAc, provided full conversion (91% isolated yield), increased the enantiomeric excess (91%), and shortened the reaction time to 2 days (entry 7), thus providing the best conditions in basic media. The Michael addition of **1a** to **2a** could also take place in acidic media (benzoic acid as additive, entry 8). Under these conditions, the reaction was faster (20 h) than in the basic medium with a good but lower isolated yield (81%) and a similar enantiomeric excess (90%).

To remove the sulfone moiety, we considered the Julia elimination of β-keto sulfones with Mg and methanol,[9] but the high reactivity of the formyl group in **4** made necessary its a priori transformation. The formation of the dimethyl acetal **5** by nucleophilic addition followed by Julia elimination[9] yielded olefin **6** in a moderate yield and high stereoselective control in a one-pot procedure (Scheme 2). On the other hand, the reduction of the aldehyde with $NaBH_4$ is also compatible with the other two reactions, allowing an efficient one-pot synthesis of the alcohol **8**. Both processes can be considered as formal alkenylation reactions of α,β-unsaturated aldehydes.[7]

The α-chiral center in the sulfone can also be eliminated by a process that involves intramolecular ketalization and subsequent dehydration of the alcohol groups in **7** (Table 2). This process provides sulfonyl hydropyrans **10**, which can be considered as precursors of polyfunctionalized pyrans, important subunits in many natural products, for example, carbohydrates, alkaloids, polyether antibiotics, and pheromones.[10]

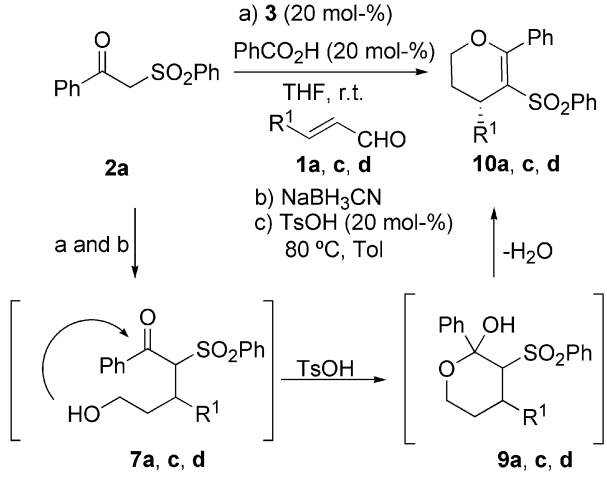
Benzoic acid was used as an additive (20 h) and the reduction was performed with $NaBH_3CN$ to yield compound **10a** in moderate yield and with excellent optical purity (entry 1, Table 2). The enantiomer of this compound (*ent*-**10a**) could be analogously obtained by using *ent*-**3** (with the *R* configuration) as the catalyst in the first step (entry 2, Table 2). Other alkyl chains can also be introduced at C-4 of the dihydropyran with excellent enantioselectivities and moderate yields (entries 3 and 4, Table 2). Nevertheless, phenyl-substituted alkene **1e** did not react under these conditions.

The use of α-sulfonylated dialkyl ketones **2b**–**d** as starting materials afforded different results to those shown in Scheme 2 and Table 2. After 6 days, the reaction of **1a** with **2b** (R^3 = H, Scheme 3) under basic conditions afforded a 1:1 mixture of cyclohexanes **11a** and **11a′**, epimers at the hydroxylic carbon (see later), in a 71% combined yield (their separation was not possible). As we could not determine the enantiomeric excess of the two diastereomers by chiral HPLC, their dehydration to only one compound **13** was necessary (see later, Scheme 4), obtained with 92% *ee*. The formation of this compound could be explained by a Michael addition reaction catalyzed by **3** followed by an



Scheme 2. Organocatalytic enantioselective alkenylation by Julia olefination.

Table 2. One-pot synthesis of hydropyrans **10a**,**c**,**d** from β-keto sulfone **2a** and unsaturated aldehydes **1**.[a]

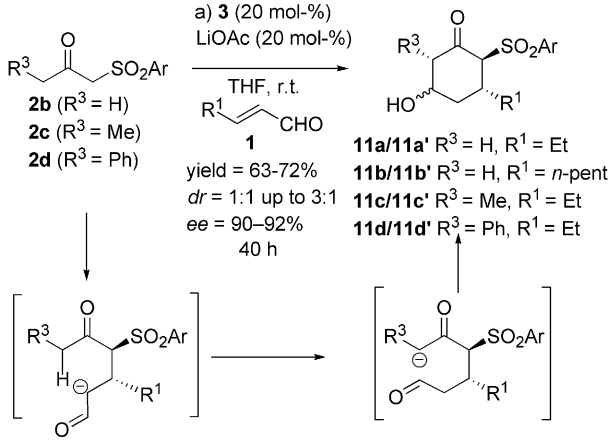


Entry	Aldehyde (R^1)	Product (% yield)	*ee* [%][b]
1	**1a** (Et)	**10a** (41)	90
2[c]	**1a** (Et)	*ent*-**10a** (44)	90
3	**1c** (*n*Pr)	**10c** (46)	90
4	**1d** (*n*Bu)	**10d** (42)	91
5	**1e** (Ph)	n.r.[d]	–

[a] Performed with **2a** (0.20 mmol), **1** (0.4 mmol), $PhCO_2H$ (20 mol-%), and catalyst **3** (10 mol-%) in THF (0.2 mL). [b] The enantiomeric excess was determined by chiral stationary phase HPLC. [c] This reaction was carried out with the *ent*-**3** catalyst (*R* configuration). [d] No reaction.

interchange of protons, which makes possible an intramolecular aldol reaction with low diastereoselectivity that affords mixtures of **11a/11a′**, which are epimers at the alcohol moiety.

We followed the reaction by ^1H NMR spectroscopy to check that the starting sulfone **2b** had disappeared after 40 h. When we tried to isolate the Michael adduct (with

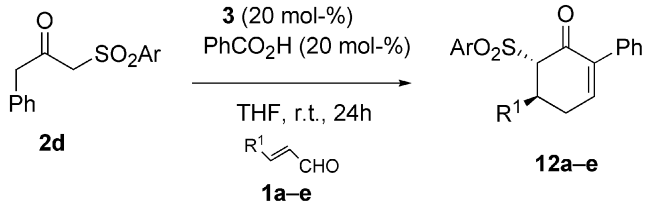


Scheme 3. Synthesis of six-membered rings with three and four chiral centers.

silica gel neutralized with Et_3N), we observed its instantaneous transformation into the same mixture **11a** and **11a′** (the reaction occurred during the purification process). This result is similar in terms of yield and enantioselectivity to those obtained directly after 6 days with LiOAc, thus providing a faster method to obtain the same compounds. Other keto sulfones, such as **2c** (R^3 = Me) and **2d** (R^3 = Ph), showed the same evolution, giving mixtures of **11c/11c′** and **11d/11d′** under similar conditions. In both cases, the enantioselectivities and yields were similar to those obtained with **2b**, whereas a slightly better diastereoselectivity was achieved with **2d** (*dr* = 3:1, R^3 = Ph).

Interestingly, when the reactions of **2d** (R^3 = Ph) with aldehydes **1a**–**e** were performed in acidic media ($PhCO_2H$ as additive instead of LiOAc), we observed a faster reaction that yielded cyclohexenones **12a**–**e** as the only products (Table 3). This indicates that the product could occur by a Michael–aldol/dehydration tandem process[11] under mild conditions in good yields and diastereoselectivities (*trans* compounds were obtained as the major products).

Table 3. Scope of various aldehydes in a tandem process.[a]



Entry	Aldehyde (R^1)	Additive	Product (% yield)	*dr*[b]	*ee* [%][c]
1	**1a** (Et)	$PhCO_2H$	**12a** (65)	92:8	80
2	**1b** (Me)	$PhCO_2H$	**12b** (68)	90:10	92
3	**1c** (*n*Pr)	$PhCO_2H$	**12c** (68)	92:8	90
4	**1d** (*n*Bu)	$PhCO_2H$	**12d** (63)	90:10	94
5	**1e** (*n*-Pent)	$PhCO_2H$	**12e** (60)	91:9	92
6	**1f** (Ph)	LiOAc	n.r.[d]	–	–
7	**1f** (Ph)	$PhCO_2H$	n.r.[d]	–	–

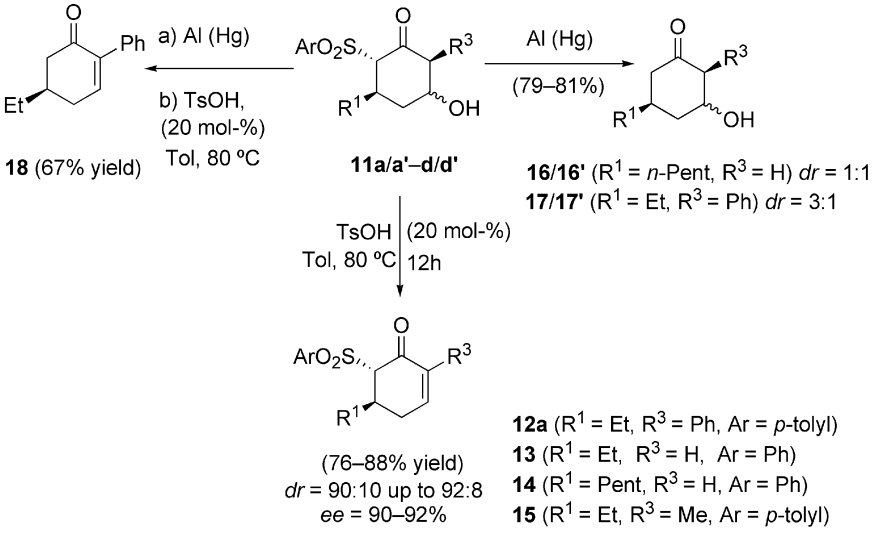
[a] Performed with **2d** (0.20 mmol), **1** (0.40 mmol), $PhCO_2H$ (20 mol-%), and catalyst **3** (20 mol-%) in THF (0.2 mL). [b] Diastereomeric ratio of the epimers at the sulfonylated carbon, as determined by ^1H NMR spectroscopy. [c] The enantiomeric excess was determined by chiral HPLC. [d] No reaction.

The yields and enantioselectivities are almost identical for all the aliphatic aldehydes, regardless of the nature of R^1 (entries 1–5, Table 3). The acidic media and the higher tendency of the phenyl derivatives to dehydrate explain this evolution. As in previous cases, aromatic α,β-unsaturated aldehydes do not react with α-sulfonylated dialkyl ketones under acidic or basic conditions (entries 6 and 7).

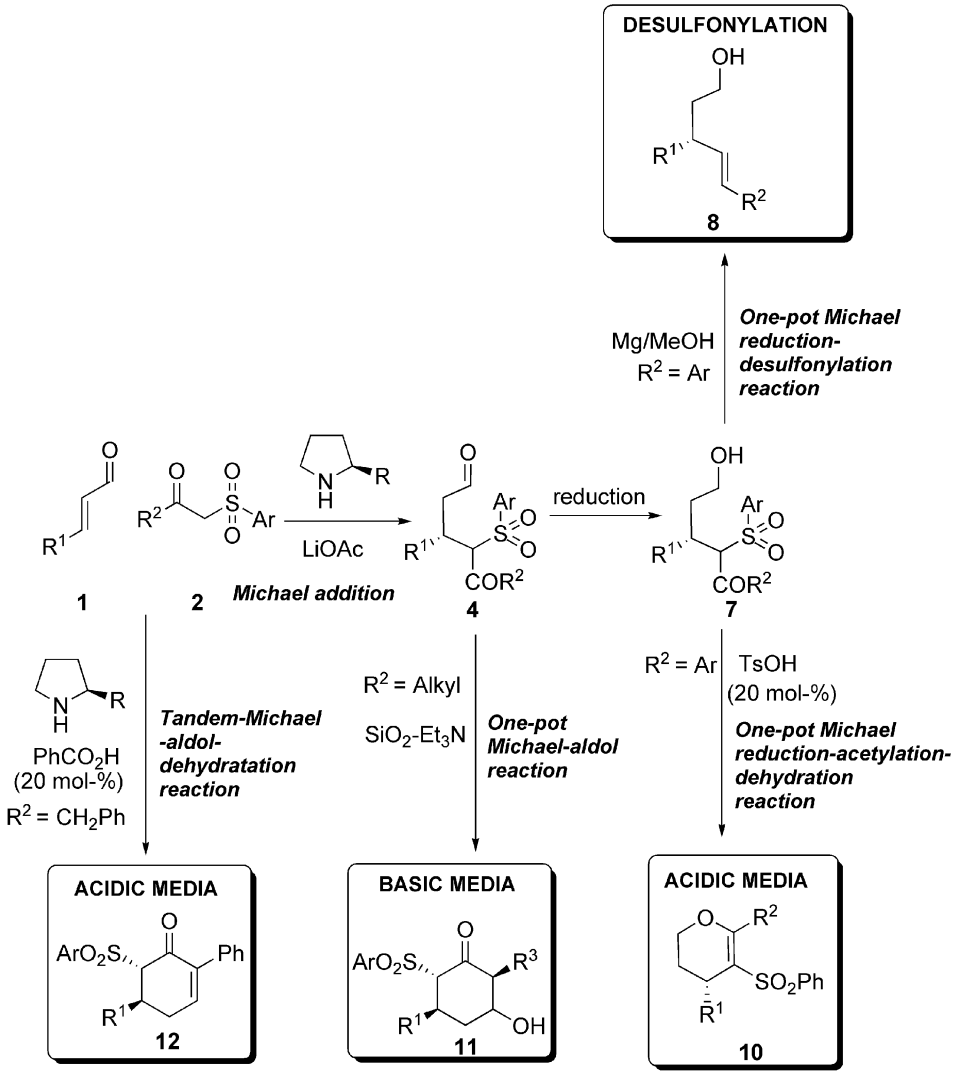
Compounds **11** were obtained as mixtures of two diastereoisomers that could be epimers at C-2 (due to the high acidity of 2-H) or C-5 (due to the low stereoselectivity of the aldol reaction). To identify the epimeric carbon we eliminated the sulfone group from a 1:1 mixture of **11b** and **11b′** (R^1 = *n*-Pent) and obtained a 1:1 mixture of **16** and **16′**. This result indicates that C-2 is not the epimeric carbon. The same conclusion was drawn from the reaction of a 3:1 mixture of **11d** and **11d′**, which afforded the same 3:1 mixture of **17** and **17′**. This means that the hydroxylic carbon (C-4) in compounds **11** is the epimeric carbon. As the mixtures of **11** and **11′** could not be easily separated, we decided to eliminate the hydroxy group to solve the problem of the mixture of the diastereoisomers. In this way, dehydration in an acidic medium would provide diastereomerically pure α,β-unsaturated ketones **12a**, **13**–**15** with high optical purity (the same as that of the starting **11**). The reaction of the 1:1 diastereomeric mixture **11d/11d′** with TsOH in toluene (80 °C) afforded **12a**. Unfortunately, this compound was also obtained as a mixture of diastereoisomers (*dr* = 90:10) in a thermodynamic equilibrium easily established due to the high acidity of the proton of the β-keto sulfone moiety. Similar results were obtained with **11a/11a′**, **11b/11b′**, and **11c/11c′**, which yielded compounds **13**, **14**, and **15**, respectively, in yields ranging between 76 and 88% (Scheme 4). The *ee* values of the resulting cyclohexenones are very high and similar to those of the starting cyclohexanones. Thus, desulfonylation and dehydration can be run as a one-pot process with the epimeric mixtures of **11** to obtain 2,5-disubstituted cyclohexenones with high optical purity. This is illustrated with the reaction of **11d/11d′**, which furnished **18** (Scheme 4).

The absolute configuration of cyclohexane **11d** (major diastereoisomer), which contains four chiral centers, was unequivocally established as 2*S*,3*R*,5*R*,6*S* (see the Supporting Information) in view of the low value obtained for the Flack parameter (0.004) in its X-ray structure.[12] The other compounds were assumed to be identical because they followed the same stereochemical course in this reaction, yielding the same configuration as at the chiral center at the α position of the sulfone moiety and at the β position of the aldehyde.

In Scheme 5 we have summarized how slight modifications to the reaction conditions are able to produce significant changes in the reaction pathways and thereby afford different compounds. When the Michael addition was car-



Scheme 4. Synthesis of optically active cyclohexenones.



Scheme 5. Summary of the different β-keto sulfones reactions.

ried out in the presence of benzoic acid and R^2 was a benzyl group, the adduct **4** could not be isolated because it suffers a tandem intramolecular aldol/dehydration process (favored by conjugation) to afford compounds **12**. In contrast, the reactions of substrates with R^2 = alkyl, conducted with LiOAc, yielded compounds **4**, which, after purification with neutralized silica gel, evolved to cyclohexanones **11** as a consequence of an intramolecular aldol reaction without dehydration. The in situ reduction of adducts **4** followed by acidic treatment of the reaction crude containing **7** yielded dihydropyrans **10** (hemiacetalization and further dehydration), whereas if the crude **7** was exposed to reductive conditions, β-alkenylation product **8** was formed by a classic Julia olefination process.[9]

Conclusions

The α-sulfonyl group is a good activator of ketones and allows the β-alkylation of unsaturated aldehydes with the ketone moiety (CH_2–CO–R) in organocatalytic processes. The resulting products from the addition of β-keto sulfones are highly versatile intermediates able to participate in diverse tandem and one-pot reactions to afford products with significant structural differences by introducing small changes in the starting materials and/or in the experimental protocol.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were acquired with a Bruker 300 spectrometer at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$: 7.26 ppm for ^{1}H NMR; $CDCl_3$: 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired in broad-band decoupled mode. Analytical thin-layer chromatography (TLC) was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. The reaction products were purified by flash chromatography (FC) using silica gel (Merck 60) that had previously been neutralized with 10 mol-% of Et_3N in hexane. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. The enantiomeric excesses (*ee*) of the

products were determined by chiral stationary phase HPLC (Daicel Chiralpak AD or Daicel Chiralcel IC columns). Catalyst **3** and all the starting materials were purchased from Aldrich. Compounds **2c**–**d** have previously been synthesized.[13]

General Procedure for the Synthesis of Compound 4a (see Table 1): The α,β-unsaturated aldehyde **1a** (0.4 mmol) was added to a stirring solution of catalyst **3** (0.02 mmol), additive (0.02 mmol), and the corresponding sulfone **2a** (0.2 mmol) in the indicated solvent (0.2 mL; Table 1) in an ordinary vial at room temperature. After the complete consumption of the sulfone derivative (as monitored by ^{1}H NMR spectroscopy; time is indicated in Table 1), the solvent was eliminated under reduced pressure. Then the crude was purified by FC (EtOAc/hexane = 2:3) to give the pure compound.

(4*R*/4*S*,3*S*)-3-Ethyl-5-oxo-5-phenyl-4-(phenylsulfonyl)pentanal (4a/4a′): The product was obtained following the standard procedure as a colorless oil (63 mg, 91% yield) after FC. The *ee* was determined by HPLC by derivatization to the product **6** (*ee* = 91%, see below). $[\alpha]_D^{20}$ = –10.0 (*c* = 1.0, CH_2Cl_2). First diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 9.83 (s, 1 H, CHO), 7.83–7.33 (m, 10 H, Ar), 5.59 (d, *J* = 9.4 Hz, 1 H, 4-H), 3.27–3.04 (m, 1 H, 2-H), 2.85–2.77 (m, 1 H, 2-H), 2.50 (dd, *J* = 18.8, *J* = 7.8 Hz, 1 H, 3-H), 1.63–1.52 (m, 2 H, CH_2), 0.80 (t, *J* = 7.5 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.7, 193.0, 137.6, 136.8, 133.7, 133.6, 129.2, 128.7, 128.5, 128.1, 70.5, 42.5, 35.1, 24.0, 11.1 ppm. Second diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 9.69 (s, 1 H, CHO), 7.83–7.33 (m, 10 H, Ar), 5.34 (d, *J* = 4.9 Hz, 1 H, 4-H), 3.27–3.04 (m, 1 H, 2-H), 2.95–2.87 (m, 1 H, 3-H), 2.95–2.87 (m, 1 H, 2-H), 1.52–1.42 (m, 2 H, CH_2), 0.90 (t, *J* = 7.3 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.4, 192.60, 138.0, 137.0, 133.8, 133.7, 129.0, 128.5, 128.4, 128.2, 69.8, 44.2, 34.2, 25.3, 10.9 ppm. MS (TOF ES$^+$): calcd. for $C_{19}H_{19}O_4S$ [M – H] 343.1040; found 343.1007.

Procedure for the Synthesis of Compounds 6 and 8 (see Scheme 2): The corresponding aldehyde (0.4 mmol) was added to a stirring solution of catalyst **3** (0.02 mmol), 2-(phenylsulfonyl)acetophenone (0.2 mmol), and LiOAc (0.02 mmol) in THF (0.2 mL) in an ordinary vial at room temperature. After the complete consumption of the 2-(phenylsulfonyl)acetophenone (as monitored by ^{1}H NMR spectroscopy), MeOH (1 mL) and $BF_3{\cdot}Et_2O$ (10 mol-%) were added for compound **6** or $NaBH_4$ (5.0 equiv.) for compound **8**. The reaction was followed by ^{1}H NMR spectroscopy and when it was finished, the reaction mixture was extracted with AcOEt (2 × 5 mL) and washed with water (2 × 5 mL). Then the solvent was eliminated under reduced pressure. Next, the crude mixture was treated with activated magnesium (10 equiv.) in MeOH (5 mL) overnight. Then the crude was purified by FC (hexane/AcOEt = 2:1) to give the pure compound.

(*R*,*E*)-(3-Ethyl-5,5-dimethoxypent-1-enyl)benzene (6): The product was obtained following the standard procedure as a mixture of diastereoisomers (95:5) as a colorless oil (19 mg, 40% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{minor} = 3.9 min, τ_{major} = 5.6 min (90% *ee*). $[\alpha]_D^{20}$ = –2.3 (*c* = 0.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3407, 2927, 1737, 1672, 1458, 1127 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.30–7.20 (m, 4 H, Ar), 7.15–7.12 (m, 1 H, Ar), 6.30 (d, *J* = 15.8 Hz, 1 H, 1-H), 5.89 (dd, *J* = 15.8, 8.2 Hz, 1 H, 2-H), 4.34 (dd, *J* = 7.4, 7.4 Hz, 1 H, 5-H), 3.26 (s, 3 H, MeO), 3.23 (s, 3 H, MeO), 2.42–2.26 (m, 1 H, 4-H), 1.93–1.71 (m, 1 H, 4-H), 1.60–1.48 (m, 3 H, 3-H, CH_2-CH_3), 0.75 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.1, 134.3, 131.2, 129.3, 129.0, 127.8, 104.1, 42.3, 39.0, 30.1, 29.8, 10.6 ppm. MS (TOF ES$^+$): calcd. for $C_{15}H_{23}O_2$ [M + H]$^+$ 235.0603; found 235.0593.

(*R*,*E*)-3-Methyl-5-phenylpent-4-en-1-ol (8): The product was obtained as a single diastereoisomer following the standard procedure as a colorless oil (16 mg, 46% yield) after FC (AcOEt/hexane = 2:1). The *ee* value was determined by HPLC using a Chiralpak OD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{major} = 8.1 min, τ_{minor} = 10.4 min (88% *ee*). $[\alpha]_D^{20}$ = –15.4 (*c* = 0.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3147 (br s), 2933, 1681, 1493, 1127 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.29–7.18 (m, 4 H, Ar), 7.15–7.12 (m, 1 H, Ar), 6.30 (d, *J* = 15.8 Hz, 1 H, 1-H), 6.02 (dd, *J* = 15.8, 8.2 Hz, 1 H, 2-H), 3.63 (t, *J* = 6.4 Hz, 2 H, CH_2-O), 2.47–2.38 (m, 1 H, 3-H), 1.63–1.57 (m, 2 H, 4-H), 1.05 (dd, *J* = 6.8, 2.0 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.1, 135.5, 128.2, 128.1, 126.6, 125.6, 60.8, 39.3, 33.8, 20.4 ppm. MS (TOF ES$^+$): calcd. for $C_{12}H_{17}O$ [M + H]$^+$ 177.1279; found 177.1275.

General Procedure for the Synthesis of the Dihydropyrans 10 (see Table 2): The corresponding aldehyde **1** (0.4 mmol) was added to a stirring solution of catalyst **3** (0.02 mmol), additive (0.02 mmol), and the corresponding sulfone **2a** (0.2 mmol) in THF (0.2 mL) in an ordinary vial at room temperature. After the complete consumption of the sulfone derivative (as monitored by ^{1}H NMR spectroscopy; time is indicated in Table 2,), THF (1 mL) and $NaBH_3CN$ (5.0 equiv.) were added. The reaction was followed by TLC and when it was finished, the reaction mixture was extracted with AcOEt (2 × 5 mL) and washed with water (2 × 5 mL). The solvent was eliminated under reduced pressure. Then the crude mixture was treated with *p*TsOH (20 mol-%) in toluene (1 mL) at 80 °C for 24 h. Finally, the crude was purified by FC (hexane/AcOEt = 4:1), to give the pure compound.

(*S*)-4-Ethyl-3,4-dihydro-6-phenyl-5-(phenylsulfonyl)-2*H*-pyran (10a): The product was obtained following the standard procedure as a colorless oil (27 mg, 41% yield) after FC. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min, τ_{minor} = 10.8 min, τ_{major} = 11.8 min (90% *ee*). $[\alpha]_D^{20}$ = +27.0 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.37–7.06 (m, 10 H, Ar), 4.26–4.11 (m, 2 H, CH_2-O), 3.00–2.90 (m, 1 H, 4-H), 2.22–2.11 (m, 1 H, 3-H), 2.01–1.85 (m, 1 H, 3-H), 1.58–1.43 (m, 2 H, CH_2-CH_3), 1.06 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 143.0, 134.1, 131.8, 129.7, 129.3, 128.1, 127.5, 127.0, 119.9, 64.1, 33.4, 28.1, 24.9, 11.5 ppm. MS (TOF ES$^+$): calcd. for $C_{19}H_{21}O_3S$ [M + H]$^+$ 329.1205; found 329.1196.

(*R*)-4-Ethyl-3,4-dihydro-6-phenyl-5-(phenylsulfonyl)-2*H*-pyran (*ent*-10a): The product was obtained following the standard procedure as a colorless oil (29 mg, 44% yield) after FC. The spectral data are identical to those of compound **10a**. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{major} = 10.8 min, τ_{minor} = 11.8 min (90% *ee*). $[\alpha]_D^{20}$ = –27.0 (*c* = 1.0, CH_2Cl_2).

(*S*)-3,4-Dihydro-6-phenyl-5-(phenylsulfonyl)-4-propyl-2*H*-pyran (10c): The product was obtained following the standard procedure as a yellow oil (32 mg, 46% yield) after FC. The *ee* was determined by HPLC using a Chiralpak IC column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min (90% *ee*). $[\alpha]_D^{20}$ = +21.8 (*c* = 1.0, CH_2Cl_2). IR (NaCl): $\tilde{\nu}$ = 2961, 1718, 1683, 1941 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.30–7.00 (m, 10 H, Ar), 4.21–4.00 (m, 2 H, CH_2-O), 3.03–2.88 (m, 1 H, 4-H), 2.14–2.02 (m, 1 H), 1.95–1.85 (m, 1 H), 1.54–1.13 (m, 4 H), 0.94 (t, *J* = 6.8 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4, 142.6, 133.7, 131.3, 129.2, 128.8, 127.7, 127.0, 126.6, 119.4, 63.6, 37.0, 31.1, 25.0, 19.7, 13.6 ppm.

MS (TOF ES$^+$): calcd. for $C_{20}H_{23}O_3S$ [M + H]$^+$ 343.1362; found 343.1370.

(*S*)-4-Butyl-3,4-dihydro-6-phenyl-5-(phenylsulfonyl)-2*H*-pyran (10d): The product was obtained following the standard procedure as a colorless oil (30 mg, 42% yield) after FC. The *ee* was determined by HPLC using a Chiralpak IC column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min (91% *ee*). $[\alpha]_D^{20}$ = +21.0 (*c* = 0.9, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2959, 2928, 1620, 1592, 1491 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.30–6.99 (m, 10 H, Ar), 4.19–4.02 (m, 2 H, CH_2-O), 2.93–2.89 (m, 1 H, 4-H), 2.13–2.08 (m, 1 H, 3-H), 1.91–1.85 (m, 1 H, 3-H), 1.47–1.07 (m, 6 H, C*H*$_2$-C*H*$_2$-C*H*$_2$-CH$_3$), 0.89 (t, *J* = 6.6 Hz, 3 H, CH_2-CH_2-CH_2-C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8, 143.0, 134.1, 131.7, 129.6, 129.2, 128.1, 127.5, 127.0, 119.9, 64.0, 34.9, 31.7, 29.2, 25.3, 22.6, 14.1 ppm. MS (TOF ES$^+$): calcd. for $C_{21}H_{25}O_3S$ [M + H]$^+$ 357.1518; found 357.1525.

General Procedure for the Synthesis of Compounds 11a–d (see Scheme 3): The corresponding aldehyde **1** (0.4 mmol) was added to a stirring solution of catalyst **3** (0.02 mmol), β-keto sulfone **2b–d** (0.2 mmol), and LiOAc (0.04 mmol) in THF (0.2 mL) in an ordinary vial at room temperature. After the complete consumption of the corresponding keto sulfone derivatives (as monitored by ^{1}H NMR spectroscopy), the crude was directly purified by FC (silica gel neutralized with 10% Et_3N in hexane; 2:1 hexane/AcOEt) to afford the pure product. The *ee* values of compounds **11a–d** were determined after derivatization to products **12a**, **13**–**15** (see Scheme 4).

(2*S*,3*R*,5*S*/5*R*)-3-Ethyl-5-hydroxy-2-(phenylsulfonyl)cyclohexanone (11a/11a′): The product was obtained as a mixture of diastereoisomers (1:1) following the standard procedure as a colorless oil (42 mg, 72% yield) after FC (AcOEt/hexane = 2:1). IR (neat): $\tilde{\nu}$ = 2964, 2930, 1671, 1596, 1148 cm^{-1}. Mixture of diastereoisomers (1:1): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 4 H, Ar), 7.67–7.64 (m, 2 H, Ar), 7.58–7.53 (m, 4 H, Ar), 4.59–4.57 (m, 1 H, 5′-H), 4.07–4.02 (m, 1 H, 5-H), 3.67 (s, 1 H), 3.57 (s, 1 H), 3.30–3.24 (m, 1 H), 3.06–2.98 (m, 1 H), 2.87–2.74 (m, 1 H), 2.56–2.36 (m, 1 H), 2.16–1.74 (m, 4 H), 1.67–1.53 (m, 4 H), 1.37–1.20 (m, 4 H), 0.94–0.83 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 200.5, 137.9, 137.7, 134.3, 134.2, 129.4, 129.3, 128.4, 128.1, 76.5, 76.4, 69.5, 65.9, 50.5, 48.6, 36.9, 34.7, 34.1, 32.7, 29.1, 26.5, 11.9, 11.5 ppm. MS (TOF ES$^+$): calcd. for $C_{14}H_{19}O_4S$ [M + H]$^+$ 283.1004; found 283.1014.

(2*S*,3*R*,5*S*/5*R*)-5-Hydroxy-3-pentyl-2-(phenylsulfonyl)cyclohexanone (11b/11b′): The product was obtained as a mixture of diastereoisomers (1:1) following the standard procedure as a colorless oil (41 mg, 63% yield) after FC (AcOEt/hexane = 2:1). IR (neat): $\tilde{\nu}$ = 2956, 2858, 1714, 1674, 1309 cm^{-1}. Mixture of diastereoisomers (1:1): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.79 (m, 4 H, Ar), 7.68–7.65 (m, 2 H, Ar), 7.59–7.54 (m, 4 H, Ar), 4.61–4.59 (m, 1 H, 5-H), 4.11–4.00 (m, 1 H, 5′-H), 3.68 (s, 1 H), 3.55 (s, 1 H), 3.31–3.25 (m, 1 H), 3.08–2.99 (m, 1 H), 2.88–2.82 (m, 1 H), 2.59–2.40 (m, 1 H), 2.07–1.55 (m, 8 H), 1.25–1.86 (m, 16 H), 0.86–0.84 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.1, 200.5, 137.9, 137.8, 134.3, 134.3, 129.4, 129.3, 128.5, 128.4, 76.5, 76.4, 69.5, 66.2, 50.5, 48.6, 36.1, 35.3, 34.6, 33.4, 33.1, 32.9, 31.3, 31.2, 27.0, 26.5, 22.5, 22.4, 13.9, 13.8 ppm. MS (TOF ES$^+$): calcd. for $C_{17}H_{25}O_4S$ [M + H]$^+$ 325.1637; found 325.1640.

(2*S*,3*R*,5*R*/5*S*,6*S*)-3-Ethyl-5-hydroxy-6-methyl-2-tosylcyclohexanone (11c/11c′): The product was obtained as a mixture of diastereoisomers (1:1) following the standard procedure as a colorless oil (39 mg, 65% yield) after FC (AcOEt/hexane = 2:1). Mixture of diastereoisomers (1:1): ^{1}H NMR ($CDCl_3$): δ = 7.67 (d, *J* = 7.8 Hz, 4 H, Ar), 7.34 (d, *J* = 7.4 Hz, 4 H, Ar), 4.37–4.31 (m, 1 H, OH), 4.13–4.06 (m, 1 H, OH), 3.73 (s, 1 H), 3.62 (s, 1 H), 3.38–3.37 (m, 1 H), 3.13–3.02 (m, 1 H), 2.70–2.50 (m, 6 H), 2.42 (s, 6 H), 1.98–1.92 (m, 1 H), 1.78–1.73 (m, 1 H), 1.27–0.77 (m, 16 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.7, 202.1, 145.4, 145.3, 135.1, 134.8, 129.9, 129.8, 128.3, 128.2, 77.7, 75.8, 72.0, 72.0, 53.6, 49.2, 38.7, 34.7, 34.3, 32.6, 29.1, 26.4, 21.6, 12.2, 11.5, 10.5, 10.4 ppm. MS (TOF ES$^+$): calcd. for $C_{16}H_{22}O_4NaS$ [M + Na]$^+$ 333.1131; found 333.1127.

(2S,3*R*,5*R*/5*S*,6*S*)-3-Ethyl-5-hydroxy-6-phenyl-2-tosylcyclohexanone (11d/11d′): The product was obtained as a mixture of diastereoisomers (3:1) following the standard procedure as a colorless oil (49 mg, 65% yield) after FC (AcOEt/hexane = 2:1). $[\alpha]_D^{20}$ = +31.7 (*c* = 0.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1714, 1672, 1209 cm^{-1}. Major diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 7.63 (d, *J* = 8.3 Hz, 2 H, Ar), 7.32–7.20 (m, 5 H, Ar), 7.09 (d, *J* = 6.6 Hz, 2 H), 4.18 (d, *J* = 10.0 Hz, 1 H, 5-H), 4.11–4.05 (m, 1 H, OH), 3.70 (s, 1 H, 2-H), 2.80–2.78 (m, 1 H, 4-H), 2.70–2.60 (m, 1 H, 4-H), 2.34 (s, 3 H, C*H*$_3$-C_6H_4-SO_2), 2.33–2.10 (m, 1 H), 2.00–1.80 (m, 1 H), 1.50–1.31 (m, 2 H, C*H*$_2$-CH_3), 0.91 (t, *J* = 7.4 Hz, 3 H, CH_2-C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.2, 130.8, 129.9, 129.7, 128.8, 128.3, 127.0, 126.1, 124.5 70.6, 65.4, 50.1, 37.7, 32.8, 26.3, 21.8, 11.2 ppm. MS (TOF ES$^+$): [calcd. for $C_{21}H_{24}O_4NaS$ M + Na]$^+$ 395.1287; found 395.1282.

General Procedure for the Synthesis of Compounds 12a–e (see Table 3): The corresponding aldehyde (0.4 mmol) was added to a stirring solution of catalyst **3** (0.04 mmol), keto sulfone **2d** (0.2 mmol), and benzoic acid (0.04 mmol) in THF (0.2 mL) in an ordinary vial at room temperature. After the complete consumption of the corresponding keto sulfone derivatives (as monitored by ^{1}H NMR spectroscopy, about 24 h) the crude was directly purified by FC (hexane/AcOEt = 2:1) to afford the pure products.

(5*R*,6*S*)-5-Ethyl-2-phenyl-6-tosylcyclohex-2-enone (12a): The product was obtained following the standard procedure as a colorless oil (46 mg, 65% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{major} = 25.2 min, τ_{minor} = 30.0 min (80% *ee*). $[\alpha]_D^{20}$ = –16.8 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2964, 2930, 1668, 1280, 1146 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2 H, Ar), 7.35–7.21 (m, 7 H, Ar), 7.04–7.00 (m, 1 H, 3-H), 3.88 (s, 1 H, 6-H), 3.38–3.35 (m, 1 H, 4-H), 3.31–3.01 (m, 1 H, 4-H), 2.51–2.43 (m, 1 H, 5-H), 2.44 (s, 3 H, C*H*$_3$-C_6H_4-SO_2), 1.63–1.50 (m, 2 H, C*H*$_2$-CH_3), 0.99 (t, *J* = 7.4 Hz, 3 H, CH_2-C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 187.9, 147.3, 145.1, 139.2, 135.7, 135.6, 129.8, 128.7, 128.4, 128.1, 127.8, 75.3, 29.7, 28.7, 26.8, 21.7, 11.7 ppm. MS (TOF ES$^+$): calcd. for $C_{21}H_{22}O_3NaS$ [M + Na]$^+$ 377.1181; found 377.1176.

(5*R*,6*S*)-5-Methyl-2-phenyl-6-tosylcyclohex-2-enone (12b): The product was obtained following the standard procedure as a colorless oil (60 mg, 68% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 80:20); flow rate: 1.0 mL/min; τ_{major} = 9.2 min, τ_{minor} = 15.0 min (92% *ee*). $[\alpha]_D^{20}$ = –27.7 (*c* = 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2 H, Ts), 7.35–7.25 (m, 7 H, Ar and Ts), 7.04–7.00 (m, 1 H, 3-H), 3.80 (s, 1 H, 6-H), 3.44–3.41 (m, 1 H, 4-H), 3.36–3.30 (m, 1 H, 4-H), 2.48–2.32 (m, 1 H, 5-H), 2.45 (s, 3 H, C*H*$_3$-C_6H_4-SO_2), 1.24 (d, *J* = 7.3 Hz, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9, 146.9, 145.2, 139.0, 135.7, 135.6, 129.8, 128.7, 128.4, 128.1, 127.9, 76.4, 31.0, 28.7, 21.7, 20.4 ppm. MS (TOF ES$^+$): calcd. for $C_{20}H_{20}O_3NaS$ [M + Na]$^+$ 363.1025; found 363.1034.

(5*R*,6*S*)-2-Phenyl-5-propyl-6-tosylcyclohex-2-enone (12c): The product was obtained following the standard procedure as a colorless

oil (50 mg, 68% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{major} = 7.3 min, τ_{minor} = 8.1 min (90% *ee*). $[\alpha]_D^{20}$ = –24.4 (*c* = 0.9, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2960, 2931, 2873, 1670, 1146 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 2 H, Ts), 7.29–7.19 (m, 7 H, Ar and Ts), 6.97–6.95 (m, 1 H, 3-H), 3.79 (s, 1 H, 6-H), 3.33–3.23 (m, 1 H, 1-H), 3.10–2.98 (m, 1 H, 4-H), 2.43–2.32 (m, 1 H, 5-H), 2.39 (s, 3 H, CH_3-C_6H_4-SO_2), 1.47–1.28 (m, 4 H, CH_2-CH_2-CH_3), 0.84 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9, 147.3, 145.1, 139.2, 135.8, 135.7, 129.8, 128.7, 128.4, 128.1, 127.9, 75.4, 35.8, 33.4, 29.1, 21.7, 20.2, 13.7 ppm. MS (TOF ES^+): calcd. for $C_{22}H_{24}O_3NaS$ $[M + Na]^+$ 391.1338; found 391.1330.

(5*R*,6*S*)-5-Butyl-2-phenyl-6-tosylcyclohex-2-enone (12d): The product was obtained following the standard procedure as a colorless oil (41 mg, 63% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{minor} = 25.3 min, τ_{major} = 38.9 min (94% *ee*). $[\alpha]_D^{20}$ = –13.4 (*c* = 0.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2958, 2856, 1716, 1670, 1144 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.95 (d, *J* = 8.4 Hz, 2 H, Ts), 7.29–7.19 (m, 7 H, Ar and Ts), 6.97–6.95 (m, 1 H, 3-H), 3.79 (s, 1 H, 6-H), 3.33–3.23 (m, 1 H, 1-H), 3.10–2.98 (m, 1 H, 4-H), 2.43–2.32 (m, 1 H, 5-H), 2.39 (s, 3 H, CH_3-C_6H_4-SO_2), 1.47–1.28 (m, 6 H, CH_2-CH_2-CH_2-CH_3), 0.84 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_2-CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9, 147.3, 145.1, 139.2, 135.8, 135.7, 129.8, 128.7, 128.4, 128.1, 127.9, 75.4, 33.4, 29.3, 29.1, 22.4, 21.7, 20.2, 13.9 ppm. MS (TOF ES^+): calcd. for $C_{23}H_{26}O_3NaS$ $[M + Na]^+$ 405.1494; found 405.1498.

(5*R*,6*S*)-5-Pentyl-2-phenyl-6-tosylcyclohex-2-enone (12e): The product was obtained following the standard procedure as a colorless oil (48 mg, 60% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{minor} = 24.8 min, τ_{major} = 28.3 min (92% *ee*). $[\alpha]_D^{20}$ = –22.6 (*c* = 1.6, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1670, 1597, 1144 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.60 (d, *J* = 8.4 Hz, 2 H, Ts), 7.27–7.13 (m, 7 H, Ts and Ar), 7.03–7.01 (m, 1 H, 3-H), 3.76 (s, 1 H, 6-H), 3.28–3.19 (m, 1 H, 4-H), 3.05–2.94 (m, 1 H, 4-H), 2.40–2.32 (m, 1 H, 5-H), 2.34 (s, 3 H, CH_3-C_6H_4-SO_2), 1.21–1.06 (m, 8 H, CH_2-CH_2-CH_2-CH_2-CH_3), 0.84 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_2-CH_2-CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9, 147.4, 145.1, 139.2, 135.7, 135.6, 129.8, 128.7, 128.4, 128.1, 127.9, 75.4, 33.7, 33.6, 31.4, 29.2, 26.7, 22.4, 21.7, 13.9 ppm. MS (TOF ES^+): calcd. for $C_{24}H_{28}O_3NaS$ $[M + Na]^+$ 419.1651; found 419.1635.

General Procedure for the Synthesis of 12a and 13–15 (see Scheme 4): The corresponding cyclohexanone (0.2 mmol) was added to a stirring solution of TsOH (0.04 mmol) in toluene (1 mL) in an ordinary vial and heated at 80 °C overnight. The crude was directly purified by FC (hexane/AcOEt = 2:1) to afford the pure products (see below).

(5*R*,6*S*)-5-Ethyl-6-(phenylsulfonyl)cyclohex-2-enone (13): The product was obtained following the standard procedure as a colorless oil (42 mg, 76% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{minor} = 11.1 min, τ_{major} = 13.6 min (92% *ee*). $[\alpha]_D^{20}$ = –9.7 (*c* = 1.4, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2966, 2935, 1716, 1673, 1148 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.80 (d, *J* = 7.2 Hz, 2 H, Ar), 7.65 (tt, *J* = 7.4, 1.2 Hz, 1 H, Ar), 7.55 (dt, *J* = 7.2, 1.4 Hz, 2 H, Ar), 7.04–6.98 (m, 1 H, 3-H), 6.10 (dd, *J* = 10.4, 3.0 Hz, 2-H), 3.72 (s, 1 H, 6-H), 3.21–3.10 (m, 1 H, 4-H), 2.97 (q, *J* = 6.8 Hz, 1 H, 4-H), 2.38–2.32 (m, 1 H, 5-H), 1.58–1.41 (m, 2 H, CH_2-CH_3), 0.94 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.6, 150.2, 138.4 134.0, 129.1, 128.6, 128.4, 74.1, 35.0, 27.9, 26.5, 11.7 ppm. MS (TOF ES^+): calcd. for $C_{14}H_{17}O_3S$ $[M + H]^+$ 265.0898; found 265.0898.

(5*R*,6*S*)-5-Pentyl-6-(phenylsulfonyl)cyclohex-2-enone (14): The product was obtained following the standard procedure as a colorless oil (50 mg, 82% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{major} = 9.1 min, τ_{minor} = 10.4 min (92% *ee*). $[\alpha]_D^{20}$ = –15.4 (*c* = 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 7.75 (d, *J* = 7.2 Hz, 2 H, Ar), 7.61 (tt, *J* = 7.4, 1.2 Hz, 1 H, Ar), 7.49 (dt, *J* = 7.2, 1.4 Hz, 2 H, Ar), 6.97–6.92 (m, 1 H, 3-H), 6.04 (dd, *J* = 10.4, 3.0 Hz, 2-H), 3.64 (s, 1 H, 6-H), 3.15–3.05 (m, 1 H, 4-H), 2.97 (q, *J* = 6.8 Hz, 1 H, 4-H), 2.30–2.20 (m, 1 H, 5-H), 1.39–1.13 (m, 8 H, CH_2-CH_2-CH_2 CH_2-CH_3), 0.79 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_2-CH_2 CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.7, 150.2, 138.5 134.1, 129.1, 128.8, 128.4, 74.3, 33.5, 31.4, 30.9, 28.4, 26.8, 22.4, 13.9 ppm. MS (TOF ES^+): calcd. for $C_{17}H_{23}O_3S$ $[M + H]^+$ 307.1360; found 307.1362.

(5*R*,6*S*)-5-Ethyl-2-methyl-6-(*p*-tolylsulfonyl)cyclohex-2-enone (15): The product was obtained following the standard procedure as a colorless oil (49 mg, 88% yield) after FC (AcOEt/hexane = 2:1). The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH = 99:1); flow rate: 1.0 mL/min; τ_{major} = 9.9 min, τ_{minor} = 11.4 min (90% *ee*). $[\alpha]_D^{20}$ = –11.6 (*c* = 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 7.64 (d, *J* = 7.9 Hz, 2 H, Ts), 7.61 (d, *J* = 7.9 Hz, 2 H, Ar), 6.75–6.71 (m, 1 H, 3-H), 3.72 (s, 1 H, 6-H), 3.18–3.08 (m, 1 H, 4-H), 2.91 (q, *J* = 6.8 Hz, 1 H, 4-H), 2.44 (s, 3 H, CH_3-C_6H_4-SO_2), 2.30–2.20 (m, 1 H, 5-H), 1.79 (t, *J* = 1.3 Hz, 3 H, CH_3-C_6H_4-SO_2), 1.52–1.38 (m, 2 H, CH_2-CH_3), 0.92 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.4, 145.0, 145.0, 135.7, 134.6, 129.7, 128.7, 74.6, 35.5, 28.0, 26.6, 21.7, 16.1, 11.7 ppm. MS (TOF ES^+): calcd. for $C_{16}H_{21}O_3S$ $[M + H]^+$ 293.1211; found 293.1218.

General Procedure for the Synthesis of 16 and 17 (see Scheme 4): A diastereomeric solution of **11** (0.2 mmol) in THF/H_2O (10 mL, 9:1) was added at room temperature to an Al (Hg) amalgam (800 mg of Al) formed a priori by a standard procedure. After completed consumption of β-keto sulfone (usually 2–4 h), the solvent was eliminated under reduced pressure and the crude was directly purified by FC to afford the pure product.

(*R*)-3-Hydroxy-5-pentylcyclohexanone (16/16′): The product was obtained from **11b/b′** following the standard procedure as a mixture of diastereoisomers (1:1) as a colorless oil (27 mg, 81% yield) after FC (AcOEt/hexane = 2:1). IR (neat): $\tilde{\nu}$ = 3434 (br s), 2962, 2927, 1709, 1496 cm^{-1}. Mixture of diastereoisomers: ^1H NMR ($CDCl_3$): δ = 3.64–3.54 (m, 2 H), 2.46–2.12 (m, 6 H, 2-H and 5-H), 2.03–1.67 (m, 8 H, CH_2-CO-CH_2), 1.33–1.24 (m, 16 H, CH_2-CH_2-CH_2-CH_2-CH_3), 0.89 (t, *J* = 7.4 Hz, 6 H, CH_2-CH_2-CH_2-CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.3 (2 C), 70.8, 67.0, 46.7, 45.3, 41.8, 41.7, 39.3, 39.2, 38.9, 38.8, 37.3, 37.2, 36.3, 35.8, 32.4, 29.6, 29.5, 27.2, 11.7, 11.4 ppm. MS (TOF ES^+): calcd. for $C_{11}H_{21}O_2$ $[M + H]^+$ 184.1456; found 184.1446.

(2*S*,5*R*)-5-Ethyl-3-hydroxy-2-phenylcyclohexanone (17/17′): The product was obtained from **11d/d′** following the standard procedure as a mixture of diastereoisomers (3:1) as a colorless oil (35 mg, 79% yield) after FC (AcOEt/hexane = 2:1). IR (neat): $\tilde{\nu}$ = 3413 (br s), 1708, 1524 cm^{-1}. Major diastereoisomer: ^1H NMR ($CDCl_3$): δ = 7.31–7.19 (m, 4 H, Ar), 7.06 (d, *J* = 7.4 Hz, 1 H, Ar), 4.19 (td, *J* = 8.7, 3.7 Hz, 1 H, CH-OH), 3.49 (d, *J* = 8.4 Hz, 1 H, 2-H), 2.55–2.49 (m, 1 H, 6-H), 2.37–2.25 (m, 1 H, 6-H), 2.14–2.04 (m, 2 H, 4-H), 1.96–1.86 (m, 1 H, 5-H), 1.34–1.25 (m, 2 H, CH_2-CH_3),

0.88 (t, J = 7.4 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.3, 135.3, 129.2, 128.8, 127.6, 71.7, 65.9, 45.4, 36.2, 34.2, 26.9, 11.8 ppm. MS (TOF ES$^+$): calcd. for $C_{14}H_{18}O_2$ $[M]^+$ 218.1307; found 218.1306.

General Procedure for the Synthesis of Compound 18 (see Scheme 4): A solution of **11d/11d′** (0.2 mmol) in THF/H_2O (10 mL, 9:1) was added at room temperature to an Al amalgam (800 mg) formed a priori by standard procedure. After the completed consumption of β-keto sulfone (usually 2–4 h), the solvent was eliminated under reduced pressure and the crude was added to a stirring solution of TsOH (0.04 mmol) in toluene (1 mL) and heated at 80 °C overnight. The crude was directly purified by FC (hexane/AcOEt = 2:1) to afford the pure product.

(*S*)-5-Ethyl-2-phenylcyclohex-2-enone (18): The product was obtained following the standard procedure as a colorless oil (27 mg, 67% yield) after FC (AcOEt/hexane = 2:1) along with an unidentified impurity. $[\alpha]_D^{20}$ = –21.6 (c = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.46–7.15 (m, 5 H, Ar), 6.88–6.84 (m, 1 H, 3-H), 2.73–2.62 (m, 2 H, 6-H), 2.33–2.18 (m, 2 H, 4-H), 1.55–1.40 (m, 3 H), 2.37–2.25 (m, 1 H), 2.14–2.04 (m, 2 H), 1.10 (t, J = 6.0 Hz, 3 H, CH_2-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 145.8, 130.1, 129.3, 125.5, 120.5, 115.2, 37.0, 30.1, 28.6, 15.4 ppm. (TOF ES$^+$): calcd. for $C_{14}H_{16}$ $[M]^+$ 200.1201; found 200.1200.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **4a**, **6**, **8**, **10a**–**d**, **11a**–**d**, **12a**–**e**, **13**–**18**, HPLC chromatographs for compounds **6**, **8**, **10a**, ***ent*-10a**, **10c**, **12a**, **12c**–**e**, **15**, and ORTEP diagram of compound **11c**.

Acknowledgments

Financial support of this work by the Ministerio de Educación y Ciencia (MEC) (CTQ-2009-12168) is gratefully acknowledged. V. M. and J. A., respectively, thank the Ministerio de Ciencia e Innovación (MICCINN) for a predoctoral fellowship and a Juan de la Cierva contract. L. M. thanks the Ministerio de Educación, Política Social y Deporte for an undergraduate fellowship.

[1] For selected references and general reviews on domino, multicomponent reactions, see: a) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001; b) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2005**, *44*, 1602; c) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; d) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; e) H.-C. Guo, J.-A. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 354; f) H. Pellissier, *Tetrahedron* **2006**, *62*, 1619; g) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143; h) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037.

[2] For selected reviews on organocatalysis, see: a) P. L. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*; Wiley-VCH, Weinheim, **2004**; c) J. Seayed, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; d) special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37*; e) B. List, J.-W. Yang, *Science* **2006**, *313*, 1584; f) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. C. Vo, *Drug Discovery Today* **2007**, *12*, 8; g) B. List, *Chem. Commun.* **2006**, 819; h) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; for general reviews of β-functionalization, see: i) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; j) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; k) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; l) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; m) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; n) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

[3] a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; b) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; c) see also ref.[11]; d) see also ref.[2n] in which Jørgensen et al. pointed out the concept of one-pot organocatalytic reactions.

[4] For some recent examples, see: a) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2009**, *48*, 6844; b) H. Jiang, N. Holub, M. W. Paixao, C. Tiberi, A. Falcicchio, K. A. Jørgensen, *Chem. Eur. J.* **2009**, *15*, 9638; c) D. Zhu, M. Lu, L. Dai, G. Zhong, *Angew. Chem. Int. Ed.* **2009**, *48*, 6089; d) A. Michrowska, B. List, *Nature Chem.* **2009**, *1*, 225; e) H. Jiang, A. Falcicchio, K. L. Jensen, M. Paixao, S. Bertelsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, *131*, 7153; f) Y.-G. Wang, T. Kumano, T. Kano, K. Maruoka, *Org. Lett.* **2009**, *11*, 2027; g) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 1304; h) O. Fadeyi, C. W. Lindsley, W. Craig, *Org. Lett.* **2009**, *11*, 943; i) J. L. García Ruano, V. Marcos, L. Marzo, J. Suanzes, J. Alemán, *Chem. Eur. J.* **2009**, *15*, 6576; j) S. Belot, K. A. Vogt, C. Besnard, N. Krause, A. Alexakis, *Angew. Chem. Int. Ed.* **2009**, *48*, 8923.

[5] For some recent publications, see: a) E. S. Gladkov, V. A. Chebanov, S. M. Desenko, O. V. Shishkin, S. V. Shishkina, D. Dallinger, C. O. Kappe, *Heterocycles* **2007**, *73*, 469; b) Y. Hua, G. C. Rich, L. N. Zakharov, *J. Am. Chem. Soc.* **2008**, *130*, 9238; c) C. Cassani, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem. Int. Ed.* **2009**, *48*, 5694; d) M. Nielsen, C. B. Jacobsen, M. W. Paixao, N. Holub, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, *131*, 10581; e) S. Kiren, A. Padwa, *J. Org. Chem.* **2009**, *74*, 7781.

[6] a) J. L. García Ruano, V. Marcos, J. Alemán, *Chem. Commun.* **2009**, 4435; see also: b) A. Landa, A. Puente, J. I. Santo, S. Vera, M. Oiarbide, C. Palomo, *Chem. Eur. J.* **2009**, *15*, 11954; c) A.-N. Alba, X. Companyó, A. Moyano, R. Rios, *Chem. Eur. J.* **2009**, *15*, 11095; for reviews on the use of the sulfonyl group in organocatalysis, see: d) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2010**, *49*, 2668; e) R. A. Andrea-Nekane, X. Companyo, R. Rios, *Chem. Soc. Rev.* DOI: 10.1039/b911852g.

[7] Recently and during the preparation of this manuscript, Jørgensen and co-workers (ref.[5d]) reported the β-alkenylation and β-alkynylation of α,β-unsaturated aldehydes. They used a modified Julia-Kocienski protocol which requires the synthesis of a β-keto-heteroarylsulfone. Our reaction proceeds from commercial β-keto sulfones in a normal Julia elimination procedure underreductive conditions (see ref.[9]).

[8] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794; see also: b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703; c) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; d) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; e) for a general review of the use of silyl diarylprolinol ethers as catalysts, see: A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922.

[9] a) M. Julia, J.-M. Paris, *Tetrahedron Lett.* **1973**, *14*, 4833; b) G. H. Lee, H. K. Lee, E. B. Choi, B. T. Kim, C. S. Pak, *Tetrahedron Lett.* **1995**, *36*, 5607.

[10] a) H. Sugimura, K. Osumi, *Tetrahedron Lett.* **1989**, *30*, 1571; b) A. K. Ghosh, R. Kawahama, *Tetrahedron Lett.* **1999**, *40*, 1093; c) A. K. Ghosh, R. Kawhama, *Tetrahedron Lett.* **1999**, *40*, 4751; d) A. K. Ghosh, C.-X. Xu, S. S. Sarang, D. Wink, *Org. Lett.* **2005**, *7*, 7; for polyfunctionalized pyran derivatives as a subunit, see: e) A. Rahman, A. Nasreen, F. Akhtar, M. S.

Shekhani, J. Clardy, M. Parvez, M. I. Choudhary, *J. Nat. Prod.* **1997**, *60*, 472; f) M. A. Brimble, H. Prabaharan, *Tetrahedron* **1998**, *54*, 2113; g) J. C. Conway, P. Quayle, A. C. Regan, C. J. Urch, *Tetrahedron* **2005**, *61*, 11910; h) R. H. Liu, W. D. Zhang, Z. B. Gu, C. Zhang, J. Su, X. K. Xu, *Nat. Prod. Res.* **2006**, *20*, 866; i) E. L. Larghi, T. S. Kaufman, *Synthesis* **2006**, *2*, 187; j) Y. Tang, J. Oppenheimer, Z. Song, L. You, X. Zhang, R. P. Hsung, *Tetrahedron* **2006**, *62*, 10785; k) M. Shoji, Y. Hayashi, *Eur. J. Org. Chem.* **2007**, 3783; l) E. D. Goddard-Boger, E. L. Ghisalberti, R. V. Stick, *Eur. J. Org. Chem.* **2007**, 3925; m) J. C. R. Brioche, K. M. Goodenough, D. J. Whatrup, J. P. A. Harrity, *J. Org. Chem.* **2008**, *73*, 1946; n) S. Kumar, W. P. Malachowski, J. B. DuHadaway, J. M. LaLonde, P. Carroll, D. Jaller, R. Metz, G. C. Prendergast, A. J. Muller, *J. Med. Chem.* **2008**, *51*, 1706.

[11] For the definitions and classifications of tandem, cascade and one-pot reactions, see: a) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365; b) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1.

[12] CCDC-724352 (for **11d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] M. W. Thomsen, B. M. Handwerker, S. A. Katz, R. B. Belser, *J. Org. Chem.* **1988**, *53*, 906.

Received: April 13, 2010
Published Online: June 25, 2010

