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Ethyl Glyoxylate *N*-Tosylhydrazone as Sulfonyl-Transfer Reagent in Base-Catalyzed Sulfa-Michael Reactions

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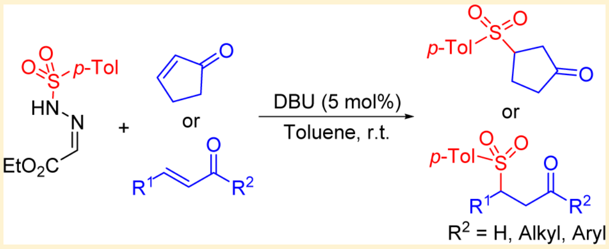
Supporting Information

ABSTRACT: Ethyl glyoxylate *N*-tosylhydrazone has been identified as an excellent sulfonyl anion surrogate in the DBU-catalyzed conjugate addition reaction with enones and enals for the synthesis of functionalized sulfones. The reaction proceeds under base-catalyzed conditions and provides a direct access to γ-keto- and γ-hydroxy sulfones in a simple and reliable way through a sulfa-Michael reaction that proceeds with high yield and chemoselectivity.

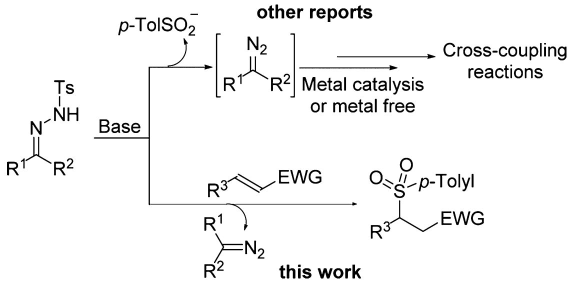


The conjugate addition of sulfur-centered nucleophiles to α,β-unsaturated carbonyl compounds or related derivatives, also regarded to as the sulfa-Michael reaction, is a powerful methodology for the formation of C−S bonds.[1] The development of new approaches to this reaction is still a field of interest due to the ubiquitous presence of sulfur-containing compounds in natural products, bioactive compounds, and materials science. In this sense, there has been intensive research over the last years showing that the sulfa-Michael reaction can be carried out with success in a catalytic way, employing either transition metals or organocatalysts to promote the reaction. However, whereas almost every possibility regarding Michael acceptors has been explored, if we consider the sulfur-centered Michael donor, most of the examples described up to date rely on the use of thiols as pronucleophiles that lead to the formation of a thioether final adduct.[2,3] In fact, sulfur compounds in different oxidation states such as sulfinates,[4] bisulfite,[5] or sulfinic acid[6] have been very rarely covered.

In this paper, we report the ability of ethyl glyoxylate *N*-tosylhydrazone to participate as a source of a sulfonyl anion equivalent for the conjugate addition reaction with enones and enals in the presence of catalytic amounts of a Brønsted base (Scheme 1).[7] Despite the fact that it is well-known in the literature that tosyl hydrazones undergo dissociation in the presence of a base to generate a sulfinate anion and a diazo compound,[8] all of the reported methodologies have used this reactivity for the generation of carbene species from the released diazoalkane reagent.[9] In this sense, there is no literature precedent illustrating the possibility of using this behavior for the generation of an *S*-based nucleophile that can be used in a subsequent transformation.[10,11]

In an initial experiment, we observed that the reaction of glyoxylate hydrazone **1a** and (*E*)-3-penten-2-one **2a** in the presence of 5 mol % of Et_3N in THF led to the formation of the desired sulfa-Michael adduct in 56% yield (entry 1 in Table 1), therefore demonstrating the viability of the reaction. In view of this preliminary result, other tertiary amine bases were tested in order to improve the yield of the process. In this sense, whereas DABCO furnished the desired sulfone in slightly better yield than Et_3N (entry 2 vs 1), the reaction with 2,2,6,6-tetramethylpiperidine did not provide any improvement (entry 3 vs 1). In a similar manner, imidazole did not afford better results (entry 4). Nevertheless, when DBU was tested, the yield of the reaction increased significantly up to 71% (entry 5). Other stronger bases were also surveyed (entries 6 and 7), observing that whereas sodium methoxide furnished a very poor result, a catalytic amount of NaH was also very effective in promoting the reaction, leading to **3a** in high yield.

Scheme 1. Different Uses of Tosylhydrazones after Base-Promoted Dissociation



Considering these results and based on the operational simplicity associated to the use of DBU when compared to NaH, we decided that the former would be the most appropriate catalyst for this reaction. Therefore, we next proceeded with the study of the influence of the solvent (entries 8−11). From these experiments, it was concluded that the reaction proceeded most efficiently in toluene (entry 9),

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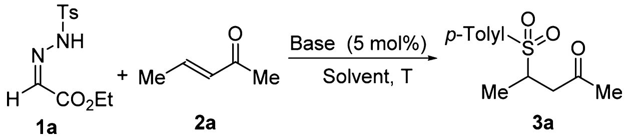
Table 1. Optimization of the Reaction Conditions[a]



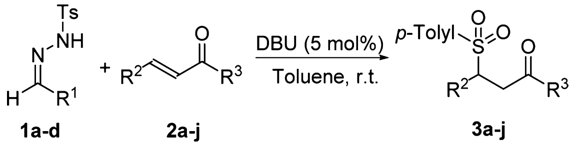
entry	base	solvent	T (°C)	yield (%)
1	Et_3N	THF	rt	56
2	DABCO	THF	rt	60
3	TMP	THF	rt	33
4	imidazole	THF	rt	32
5	DBU	THF	rt	71
6	NaOMe	THF	rt	32
7	NaH	THF	rt	68
8	DBU	hexane	rt	65
9	DBU	toluene	rt	83
10	DBU	$CHCl_3$	rt	30
11	DBU	*i*-PrOH	rt	26
12	DBU	toluene	40	79

[a] Reaction conditions: ethyl glyoxylate *N*-tosylhydrazone (**1a**) (0.30 mmol), enone (**2a**) (0.30 mmol), base (5 mol %) in 3 mL of solvent at the specified temperature.

observing low to moderate yields of **3a** both when less polar solvents like hexane or chloroform (entries 8 and 10) and when protic ones like *i*-PrOH (entry 11) were used. Finally, when the reaction was attempted at higher temperature, a similar yield of **3a** was obtained (entry 12).

Once an optimized protocol for the reaction was established, we directed our efforts to define the scope and limitations of the reaction with respect to the use of different enones as Michael acceptors. Moreover, the possibility of using other hydrazones as the sulfonyl transfer reagent was also studied. As shown in Table 2, the reaction using ethyl glyoxylate hydrazone **1a** proceeded smoothly for a set of differently substituted enones, regardless the substitution pattern at both the 1- and 3-positions. Enones with *β*-alkyl substituents reacted very efficiently, providing *β*-sulfonylated adducts **3a−d** in good yields (entries 1−4), and the results were generally moderate when aryl substituents were incorporated at *β*-position of the enone (entries 5−8) with the exception of *p*-tolyl-substituted enone **2g**, which showed the best performance of all substrates tested (entry 7). On the other hand, the reaction proceeded with high efficiency regardless the substitution at the carbonyl moiety, performing well when a bulkier ethyl substituent was introduced (entry 9) and also in the case of 1-phenyl-2-buten-1-one (**2j**) (entry 10). With respect to the hydrazone reagent, the results show the need for a hydrazone structure with an electron-withdrawing substituent at the azomethine carbon to be active as sulfonyl transfer reagent, so that a more stable diazo-compound can be generated as the other partner in the reaction. As shown in Table 2, the use of tosyl hydrazones **1c** and **1d** derived respectively from acetaldehyde and benzaldehyde (entries 12 and 13) were completely inactive in the reaction, while glyoxylic acid tosylhydrazone **1b** was still able to provide similar results to those furnished by hydrazone **1a** (entry 11).

Table 2. Scope of the Reaction: Enones as Michael Acceptors

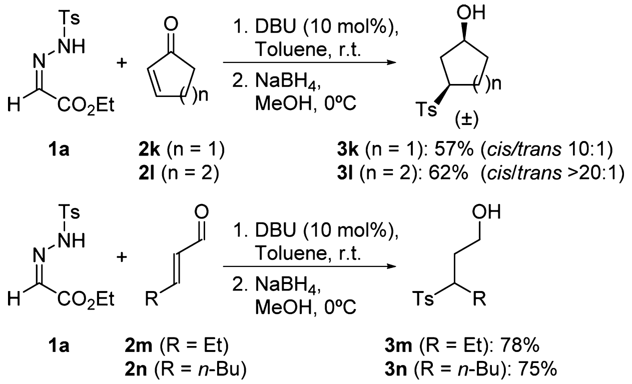


entry	R^1 (**1**)	**3**	R^2	R^3	yield[a] (%)
1	CO_2Et (**1a**)	**3a**	Me	Me	83
2	CO_2Et (**1a**)	**3b**	*n*-Pr	Me	79
3	CO_2Et (**1a**)	**3c**	*n*-Bu	Me	82
4	CO_2Et (**1a**)	**3d**	*i*-Pr	Me	68
5	CO_2Et (**1a**)	**3e**	Ph	Me	61
6	CO_2Et (**1a**)	**3f**	4-ClC_6H_4	Me	53
7	CO_2Et (**1a**)	**3g**	4-MeC_6H_4	Me	85
8	CO_2Et (**1a**)	**3h**	4-MeOC_6H_4	Me	39
9	CO_2Et (**1a**)	**3i**	Me	Et	84
10	CO_2Et (**1a**)	**3j**	Me	Ph	82
11	CO_2H (**1b**)	**3a**	Me	Me	80
12	Me (**1c**)	**3a**	Me	Me	<5
13	Ph (**1d**)	**3a**	Me	Me	<5

[a] Yield of isolated product after flash column chromatography purification.

In addition, cyclic enones such as cyclopentenone and cyclohexenone were also found to react in a very efficient manner under the optimized reaction conditions (Scheme 2), and the *in situ* reduction of the carbonyl group was necessary in order to avoid the retro-Michael reaction that led to the formation of starting materials after isolation of the *β*-sulfonylated product. In these cases, the reduction was accomplished with high levels of diastereocontrol. Moreover, *α*,*β*-unsaturated aldehydes were also studied as potential Michael acceptors observing again high yields of the overall process after in situ reduction (Scheme 2). This situation allowed the preparation of differently substituted *γ*-hydroxysulfones in one step and starting from readily available starting materials.

Scheme 2. Reactions Using Cyclic Enones and *α*,*β*-Unsaturated Aldehydes as Michael Acceptors



Several experiments have been carried out in order to obtain some insight of the possible mechanism of the reaction. On one hand, we were able to isolate ethyl diazoacetate from the reaction mixture in several occasions, which is consistent with the already reported tendency of tosyl hydrazones to dissociate in the presence of a Brønsted base to deliver a sulfinate salt and the corresponding diazoalkane. However, when we carried out the reaction between enone **2a** and sodium *p*-toluenesulfinate in the presence of both Brønsted acids or tertiary amine bases in different proportions and using a set of different solvents, we did not observe in any case the formation of any sulfa-Michael addition product. This is an indication of the participation of the hydrazone itself in the sulfur-transfer step of the catalytic cycle rather than as a simple source of sulfinate anion. Further efforts are ongoing in our laboratories in order to unveil the exact role played by these hydrazone reagents as nucleophilic sulfonyl transfer reagents. Finally, it should also be pointed out that several attempts have also been carried out in order to render this transformation enantioselective but all experiments carried out up to date using either chiral tertiary amines (cinchona alkaloids) as catalysts or under PTC conditions (cinchonidinium salts) have furnished racemic materials. Along the same line, attempts to apply the iminium activation approach to the reaction with α,β-unsaturated aldehydes using *O*-TMS diphenylprolinol as catalyst have also resulted into the formation of racemic products under all conditions tested.

In conclusion, we have demonstrated that *N*-tosylhydrazones can be used as sulfur-centered pro-nucleophiles for performing sulfa-Michael reactions with α,β-unsaturated ketones and aldehydes, providing a straightforward synthesis of γ-keto- and γ-hydroxy sulfones. Overall, the operational simplicity of the method together with the high chemical yields obtained make this methodology a strategy of choice for the direct synthesis of sulfonyl compounds.

■ EXPERIMENTAL SECTION

General Procedure for the Preparation of γ-Ketosulfones 3a−j. To a solution of (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (0.30 mmol) in toluene (3 mL) at room temperature were added DBU (0.015 mmol) and the corresponding α,β-unsaturated ketone **2a−j** (0.30 mmol), and the mixture was stirred for 3 days. Afterward, the solvent was removed under reduced pressure and reaction crude was purified by flash column chromatography to afford β-tosylated ketones **3a−j**.

*4-(p-Toluenesulfonyl)-2-pentanone (**3a**).* Following the general procedure, **3a** (60 mg, 0.25 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 83% yield as a white solid starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 3-penten-2-one **2a** (45 μL, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 3.71−3.52 (m, 1H), 3.16 (dd, *J* = 18.0, 3.4 Hz, 1H), 2.55 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.42 (s, 3H), 2.15 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.1, 144.9, 134.0, 129.9, 128.9, 55.5, 42.5, 30.4, 21.6, 14.2. IR (neat): 1715, 1286, 1140 cm^{-1}. MS (70 eV) *m/z*: 240 (M$^+$, 1), 198 (8), 156 (10), 139 (9), 119 (21), 91 (36), 85 (25), 65 (20), 43 (100). HRMS: calcd for [$C_{12}H_{17}O_3S$]$^+$ 241.0898 [M + H]$^+$, found 241.0891. Mp (hexanes/EtOAc): 79−80 °C.

*4-(p-Toluenesulfonyl)-2-heptanone (**3b**).* Following the general procedure, **1g** (64 mg, 0.24 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 79% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 3-hepten-2-one **2b** (40 μL, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 3.78−3.65 (m, 1H, CH), 3.10 (dd, *J* = 18.2, 5.2 Hz, 1H), 2.55 (dd, *J* = 18.2, 6.5 Hz, 1H), 2.43 (s, 3H), 2.15 (s, 3H), 1.82−1.69 (m, 1H), 1.52−1.10 (m, 3H), 0.82 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.1, 144.8, 134.7, 129.9, 128.8, 59.4, 41.4, 30.9, 30.2, 21.6, 19.9, 13.8. IR (neat): 1718, 1287, 1143 cm^{-1}. MS (70 eV) *m/z*: 183 (1), 150 (8), 139 (11), 119 (10), 113 (71), 91 (30), 65 (14), 55 (13), 43 (100). HRMS: calcd for [$C_{14}H_{21}O_3S$]$^+$ 269.1211 [M + H]$^+$, found 269.1208.

*4-(p-Toluenesulfonyl)-2-octanone (**3c**).* Following the general procedure, **1f** (70 mg, 0.25 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 82% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 3-octen-2-one **2c** (45 μL, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3,71−3.64 (m, 1H), 3.10 (dd, *J* = 18.2, 5.3 Hz, 1H), 2.56 (dd, *J* = 18.2, 6.4 Hz, 1H), 2.43 (s, 3H), 2.16 (s, 3H), 1.85−1.72 (m, 1H), 1.55−1.38 (m, 1H), 1.31−1.12 (m, 4H), 0.80 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.1, 144.8, 134.7, 129.8, 128.8, 59.5, 41.3, 30.2, 28.6, 28.5, 22.4, 21.6, 13.7. IR (neat): 1720, 1297, 1142 cm^{-1}. MS (70 eV) *m/z*: 183 (1), 150 (9), 139 (12), 127 (62), 119 (8), 109 (26), 91 (29), 83 (7), 65 (13), 55 (14), 43 (100). HRMS: calcd for [$C_{15}H_{23}O_3S$]$^+$:283.1368 [M + H]$^+$, found 283.1379.

*5-Methyl-4-(p-toluenesulfonyl)-2-hexanone (**3d**).* Following the general procedure, **1h** (55 mg, 0.20 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 68% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 5-methyl-3-hexen-2-one **2d** (53 μL, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 3.76 (ddd, *J* = 7.0, 4.1, 1.9 Hz, 1H), 3.08 (dd, *J* = 18.5, 7.0 Hz, 1H), 2.54 (dd, *J* = 18.5, 4.1 Hz, 1H), 2.44 (s, 3H), 2.34 (m, 1H), 2.15 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (75 MHz, CDCl$_3$): δ 204.3, 144.7, 135.7, 129.8, 128.5, 64.0, 36.7, 30.1, 26.7, 21.6, 17.5. IR (neat): 1719, 1300, 1145 cm^{-1}. MS (70 eV) *m/z*: 183 (M$^+$ − $C_5H_{10}O$, 2), 150 (6), 139 (10), 119 (7), 113 (77), 91 (27), 65 (13), 55 (6), 43 (100). HRMS: calcd for [$C_{14}H_{21}O_3S$]$^+$ 269.1211 [M + H]$^+$, found 269.1215.

*4-Phenyl-4-(p-toluenesulfonyl)-2-butanone (**3e**).*[12] Following the general procedure, **1a** (55 mg, 0.18 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 61% yield as a white solid starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 4-phenyl-3-buten-2-one **2e** (44 mg, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.43−7.07 (m, 9H), 4.70 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.58 (dd, *J* = 17.8, 4.3 Hz, 1H), 3.25 (dd, *J* = 17.8, 9.1 Hz, 1H), 2.37 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 203.4, 144.8, 133.9, 132.6, 129.7, 129.4, 129.0, 128.8, 128.5, 66.2, 41.6, 30.5, 21.6. IR (neat): 1719, 1303, 1144 cm^{-1}. MS (70 eV) *m/z*: 147 (32), 131 (17), 123 (11), 104 (23), 91 (19) 77 (13), 65 (9), 43 (100). HRMS: calcd for [$C_{10}H_{11}O$]$^+$ 147.0810 [M − $C_7H_7O_2S$]$^+$, found 147.0791. Mp (hexanes/EtOAc): 149−150 °C.

*4-(4-Chlorophenyl)-4-(p-toluenesulfonyl)-2-butanone (**3f**).* Following the general procedure, **1b** (53 mg, 0.16 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 53% yield as a white solid starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 4-(4-chlorophenyl)-3-buten-2-one **2f** (56 mg, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.23−7.16 (m, 4H), 7.06 (d, *J* = 8.5 Hz, 2H), 4.66 (dd, *J* = 9.3, 4.1 Hz, 1H), 3.57 (dd, *J* = 17.9, 4.1 Hz, 1H), 3.21 (dd, *J* = 17.9, 9.3 Hz, 1H), 2.39 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 203.0, 145.0, 140.9, 134.8, 131.2, 130.4, 129.6, 129.0, 128.7, 65.4, 41.6, 30.4, 21.7. IR (neat): 1713, 1310, 1142 cm^{-1}. MS (70 eV) *m/z*: 181 (26), 165 (27), 150 (6), 138 (16), 119 (6), 102 (12), 91 (18) 75 (7), 65 (8), 43 (100). HRMS: calcd for [$C_{10}H_{10}OCl$]$^+$ 181.0420 [M − $C_7H_7O_2S$]$^+$, found 181.0403. Mp (hexanes/EtOAc): 141−142 °C.

*4-(4-Methylphenyl)-4-(p-toluenesulfonyl)-2-butanone (**3g**).* Following the general procedure, **1c** (46 mg, 0.14 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 48% yield as a white solid starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (162 mg, 0.60 mmol), 4-(4-methylphenyl)-3-buten-2-one **2g** (50 mg, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.67 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.54 (dd, *J* = 17.7, 4.4 Hz, 1H), 3.23 (dd, *J* = 17.7, 9.2 Hz, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 203.4, 144.7, 138.8, 134.0, 129.5, 129.4, 129.2, 129.1, 65.9, 41.7, 30.5, 21.6, 21.2. IR (neat): 1721, 1284, 1141 cm^{-1}. MS (70 eV) *m/z*: 161 (70), 145 (57), 115 (29), 91 (34) 77 (4), 65 (12), 43 (100). HRMS: calcd for [$C_{11}H_{13}O$]$^+$ 161.0966 [M − $C_7H_7O_2S$]$^+$, found 161.0946. Mp (hexanes/EtOAc): 93−94 °C.

4-(4-Methoxyphenyl)-4-(p-toluenesulfonyl)-2-butanone (***3h***). Following the general procedure, **1d** (39 mg, 0.12 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 39% yield as a white solid starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 4-(4-methoxyphenyl-3-buten-2-one **2h** (54 mg, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.39 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.5 Hz, 2H), 4.65 (dd, J = 9.3, 4.3 Hz, 1H), 3.76 (s, 3H), 3.54 (dd, J = 17.6, 4.3 Hz, 1H), 3.21 (dd, J = 17.7, 9.3 Hz, 1H), 2.39 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 203.4, 159.6, 144.6, 134.0, 130.9, 129.4, 129.0, 124.6, 113.9, 65.6, 55.2, 41.7, 30.5, 21.6. IR (neat): 1720, 1301, 1142 cm^{-1}. MS (70 eV) *m*/*z*: 177 (85), 161 (22), 133 (22), 118 (8), 103 (6), 91 (28) 77 (10), 65 (11), 43 (100), 28 (6). HRMS: calcd for $[\mathrm{C_{11}H_{13}O_2}]^+$ 177.0916 [M − C$_7$H$_7$O$_2$S]$^+$, found 177.0896. Mp (hexanes/EtOAc): 136−137 °C.

5-(p-Toluenesulfonyl)-3-hexanone (***3i***). Following the general procedure, **1i** (64 mg, 0.25 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 84% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 4-hexen-3-one **2i** (38 μL, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.75 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 3.65 (dqd, J = 9.8, 6.8, 3.5 Hz, 1H), 3.15 (dd, J = 17.8, 3.5 Hz, 1H), 2.62−2.32 (m, 6H), 1.22 (d, J = 6.8 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 206.96, 144.9, 134.0, 129.9, 128.9, 55.5, 41.2, 36.6, 21.6, 14.2, 7.6. IR (neat): 1713, 1285, 1139 cm^{-1}. MS (70 eV) *m*/*z*: 225 (3), 164 (12), 139 (24), 119 (9), 99 (8), 91 (23), 69 (15), 57 (100), 39 (6), 29 (12). HRMS: calcd for $[\mathrm{C_{13}H_{19}O_3S}]^+$ 255.1055 [M + H]$^+$, found 255.1063.

1-Phenyl-3-(p-toluenesulfonyl)-1-butanone (***3j***).[13] Following the general procedure **1j** (74 mg, 0.25 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) in 82% yield as a white solid starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (81 mg, 0.30 mmol), 1-phenyl-3-buten-1-one **2j** (44 μL, 0.30 mmol), and DBU (2 mg, 0.015 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.91 (d, J = 7,9, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.62−7.31 (m, 5H), 3.82 (dqd, J = 9.9, 6.8, 2.8 Hz, 1H), 3.70 (dd, J = 17.5, 2.8 Hz, 1H), 3.15 (dd, J = 17.5, 9.9 Hz, 1H), 2.43 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 195.8, 144.9, 136.2, 134.1, 133.7, 129.9, 128.8, 128.1, 127.9, 55.9, 37.9, 21.6, 14.2. IR (neat): 1684, 1290, 1142 cm^{-1}. MS (70 eV) *m*/*z*: 197 (1), 147 (14), 131 (4), 105 (100), 91 (8), 77 (26), 65 (4), 51 (6). HRMS: calcd for $[\mathrm{C_{10}H_{11}O}]^+$ 147.0810 [M − C$_7$H$_7$O$_2$S]$^+$, found 147.0795. Mp (hexanes/EtOAc): 117−118 °C.

General Procedure for the Preparation of γ-Hydroxysulfones 3k−n. To a solution of (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **1a** (0.39 mmol) in toluene (3 mL) at room temperature DBU (0,03 mmol) and the corresponding α,β-unsaturated ketone **2k−l** (0.30 mmol) or α,β-unsaturated ketone **2m−n** (0.30 mmol) were added, and reaction mixture was stirred for 2 days. Afterward, NaBH$_4$ (0.33 mmol, 27 mg) and MeOH (1 mL) were added and the mixture stirred during 1 h at 0 °C. The mixture was quenched with addition of a saturated solution of NH$_4$Cl. The organic layer was separated and the aqueous phase extracted in CH$_2$Cl$_2$ (3 × 5 mL). The combined organic fractions were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography.

(1R,3S*)-3-(p-Toluenesulfonyl)cyclopentan-1-ol* (***3k***).[14] Following the general procedure, **3k** (40 mg, 0.17 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 2:8) in 57% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **3a** (105 mg, 0.39 mmol), cyclopent-2-enone **2k** (26 μL, 0.30 mmol), and DBU (5 mg, 0.03 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.77 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 4.42−4.16 (m, 1H), 3.70−3.44 (m, 1H), 2.91 (s, 1H), 2.43 (s, 3H), 2.35−2.04 (m, 2H), 2.00−1.59 (m, 4H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.8, 135.0, 129.9, 128.5, 72.5, 63.1, 36.1, 35.4, 24.6, 21.6. IR (neat): 3490, 1285, 1143 cm^{-1}. MS (70 eV) *m*/*z*: 240 (M$^+$, 8), 183 (10), 157 (59), 139 (23), 107 (8), 92 (76), 85 (66), 67 (100). HRMS: calcd for $[\mathrm{C_{12}H_{17}O_3S}]^+$ 241.0898 [M + H]$^+$, found 241.0885.

(1R,3S*)-3-(p-Toluenesulfonyl)cyclohexan-1-ol* (***3l***).[14] Following the general procedure, **3l** (47 mg, 0.19 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 6:4) in 62% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **3a** (105 mg, 0.39 mmol), cyclohex-2-enone **2l** (30 μL, 0.30 mmol), and DBU (5 mg, 0.03 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.71 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz), 3.53 (tt, J = 10.6, 4.0 Hz, 1H), 2.91 (tt, J = 12.3, 3.4 Hz, 1H), 2.43 (s, 3H), 2.07−2.37 (m, 2H), 2.11−1.72 (m, 3H), 1.51−1.02 (m, 4H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.8, 133.8, 129.8, 129.1, 69.3, 61.9, 59.7, 34.38, 34.35, 24.6, 22.7, 21.6. IR (neat): 3479, 1297, 1143 cm^{-1}. MS (70 eV) *m*/*z*: 254 (M$^+$, 2), 157 (41), 139 (9), 99 (27), 92 (41), 81 (100), 65 (15), 55 (17). HRMS: calcd for $[\mathrm{C_{13}H_{19}O_3S}]^+$ 255.1055 [M + H]$^+$, found 255.1065.

3-(p-Toluenesulfonyl)pentan-1-ol (***3m***). Following the general procedure, **3m** (56 mg, 0.23 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 4:6) in 77% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **3a** (105 mg, 0.39 mmol), 2-pentenal **2m** (31 μL, 0.30 mmol), and DBU (5 mg, 0.03 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.76 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 3.85 (dt, J = 12.0, 6.1 Hz, 1H), 3.79−3.60 (m, 1H), 3.18−3.00 (m, 1H), 2.44 (s, 3H), 2.25 (bs, 1H), 2.18−2.01 (m, 1H), 1.96−1.74 (m, 2H), 1.67−1.43 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.7, 134.7, 129.8, 128.9, 63.1, 59.8, 30.1, 21.8, 21.6, 11.1. IR (neat): 3447, 1282, 1141 cm^{-1}. MS (70 eV) *m*/*z*: 198 (1), 183 (3), 157 (55), 139 (16), 107 (5), 92 (61), 69 (100), 57 (6). HRMS: calcd for $[\mathrm{C_{12}H_{19}O_3S}]^+$ 243.1055 [M + H]$^+$, found 243.1037.

3-(p-Toluenesulfonyl)heptan-1-ol (***3n***). Following the general procedure, **3n** (61 mg, 0.22 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 4:6) in 75% yield as a colorless oil starting from (*Z*)-ethyl 2-(2-tosylhydrazono)acetate **3a** (105 mg, 0.39 mmol), 2-heptenal **2n** (39 μL, 0.30 mmol), and DBU (5 mg, 0.03 mmol) and using toluene (3 mL) as solvent. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.74 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 3.89−3.75 (m, 1H), 3.75−3.60 (m, 1H), 3.06−3.20 (m, 1H), 2.43 (s, 3H), 2.38 (bs, 1H), 2.09 (ddd, J = 14.8, 12.7, 6.3 Hz, 1H), 1.91−1.71 (m, 2H), 1.60−1.15 (m, 5H), 0.81 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.7, 134.5, 129.8, 128.8, 61.7, 59.7, 30.8, 28.6, 28.3, 22.4, 21.6, 13.6. IR (neat): 3501, 1285, 1139 cm^{-1}. MS (70 eV) *m*/*z*: 183 (5), 157 (73), 139 (21), 115 (43), 97 (86), 81 (10), 65 (21), 55 (100). HRMS: calcd for $[\mathrm{C_{14}H_{23}O_3S}]^+$ 271.1368 [M + H]$^+$, found 271.1348.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds prepared. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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