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Direct, organocatalytic α-sulfenylation of aldehydes and ketones

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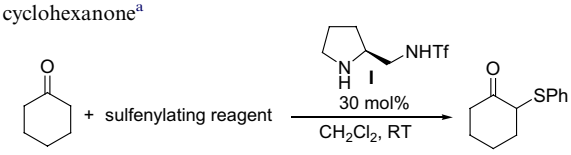
Abstract—A method for direct sulfenylation of aldehydes and ketones, catalyzed by a novel pyrrolidine trifluoromethanesulfonamide organocatalyst, has been developed. This process serves as an efficient and mild approach to the preparation of α-phenylthio-ketones and -aldehydes.

One of the important themes in contemporary organic synthesis is the development of new reactions that produce versatile building blocks from simple and readily available starting materials. α-Sulfenylated carbonyl compounds are particularly attractive synthetic intermediates since they have been used for a variety of organic transformations.[1] Among the most common methods used for the synthesis of these substrates are sulfenylation reactions of enolates[2] and S_N2 displacement reactions of α-halogenated carbonyl compounds[3] with sulfides. Most methods, including those that use sulfenylation reactions of preformed enolates[4] or enamines,[5] require multistep preparative sequences. To our knowledge, no direct, catalytic procedure for α-sulfenylation of unmodified aldehydes and ketones has been described. Recently we uncovered a simple, direct, and efficient method for the preparation of α-selenoaldehydes and ketones from aldehydes and ketones.[6,7] These α-selenenylation reactions are promoted by the respective organocatalysts L-prolinamide and pyrrolidine trifluoromethanesulfonamide **I**. In continuing efforts directed at an exploration of α-oxidation reactions of aldehydes and ketones, we observed the first examples of high yielding aldehyde and ketone α-sulfenylations. The reactions were efficiently catalyzed by the pyrrolidine trifluoromethanesulfonamide **I**,[8] in which *N*-(phenylthio)phthalimide serves as the phenylsulfenyl source. In this communication, we report the results of a detailed study of this process, which has led to the development of a direct method for organocatalytic α-sulfenylation of aldehydes and ketones.

The reaction conditions used earlier for α-selenenylation of ketones were adapted to the α-sulfenylation process.[7] Reactions of cyclohexanone with three commercially available sulfenylating reagents, *N*-(phenylthio)phthalimide, dimethyldisulfide, and diphenyldisulfides in the presence of 30 mol% pyrrolidine trifluoromethanesulfonamide **I** as the organocatalyst were probed to evaluate the sulfenylation reaction efficiencies (Table 1). The

Table 1. Effect of sulfenylating reagents on α-sulfenylation reactions of cyclohexanone[a]



Entry	Sulfenylation reagent	*t* (h)	Yield[b] (%)
1	*N*-(Phenylthio)phthalimide	23	89
2	PhSSPh	48	<10
3	MeSSMe	48	<10

[a] Reaction conditions: To a vial containing cyclohexanone (0.5 mmol), 0.5 mL of anhydrous CH_2Cl_2 and 0.1 g of 4 Å molecule sieves was added catalyst **I** (0.075 mmol) at room temperature. After 10 min vigorous stirring, sulfenylating reagent (0.25 mmol) was added. Stirring was continued for a certain period of time (see Table 1). The reaction mixture was treated with water (5 mL), then the solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography.
[b] Isolated yield.

Keywords: α-Sulfenylation; Ketones; Aldehydes; Organocatalyst; Pyrrolidine sulfonamide.
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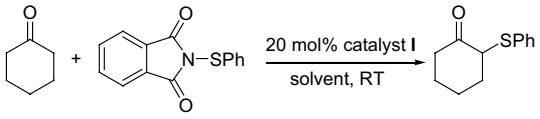
Table 2. Effect of solvents on α-sulfenylation reaction of cyclohexanone with **I**[a]



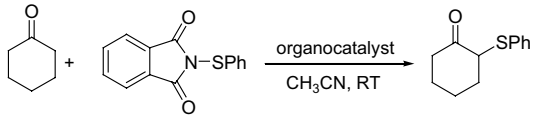
Entry	Solvent	*t* (h)	Yield[b] (%)
1	CH_2Cl_2	24	81
2	CH_3CN	4	83
3	THF	12	78
4	EtOAc	11	70
5	1,4-Dioxane	10	58
6	DMSO	24	39
7	DMF	24	39

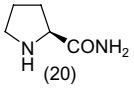
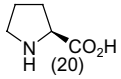
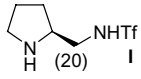
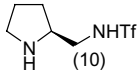
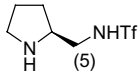
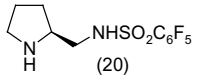
[a] Reaction conditions (see footnote in Table 1).
[b] Isolated yield.

yield of the reaction using *N*-(phenylthio)phthalimide was found to be superior to those with the other two sulfenylating reagents. Therefore, this reagent was used in subsequent reactions.

As the data in Table 2 demonstrate, the reaction medium had a great impact on the α-sulfenylation process. Reactions in CH_2Cl_2, CH_3CN, EtOAc, and THF, proceeded in high yields, while using solvents such as 1,4-dioxane, DMSO, and DMF, were less efficient. As a result, CH_3CN was selected as the solvent of choice for the subsequent studies.

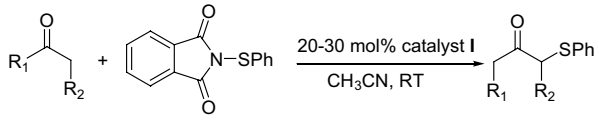
Table 3. Catalyst screening for α-sulfenylation reaction of cyclohexanone[a]

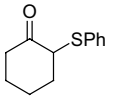
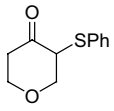
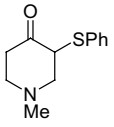
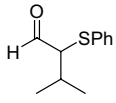
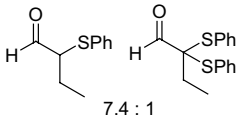
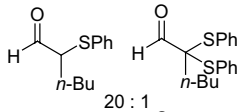
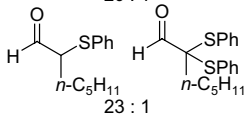
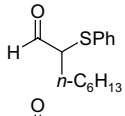
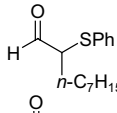
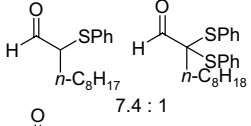
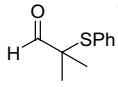


Entry	Catalyst (mol%)	*t* (h)	Yield[b] (%)
1		24	ND
2		10	66
3		4	83
4		24	48
5		24	12
6		24	<10
7		24	<10
8		24	<10

[a] Reaction conditions (see footnote in Table 1).
[b] Isolated yields.

Table 4. Pyrrolidine sulfonamide **I** catalyzed α-sulfenylation reactions of ketones and aldehydes[a]



Entry	Product	*t* (h)	Yield[b] (%)
1		4	83[c]
2		6	88[c]
3		24	60[c]
4		24	56[d]
5	 7.4 : 1	36	56[d,e]
6	 20 : 1	36	42[d,e]
7	 23 : 1	36	52[d,e]
8		30	66[d]
9		36	63[d]
10	 7.4 : 1	36	57[d,e]
11		72	46[d]

[a] Reaction conditions (see footnote in Table 1).
[b] Isolated yield.
[c] 20 mol% **I** used.
[d] 30 mol% **I** used.
[e] Molar ratio determined by ^1H NMR.

A catalyst screening study of the α-sulfenylation reaction of cyclohexanone with *N*-(phenylthio)phthalimide was performed next. A wide range of reaction yields were obtained when the pyrrolidine derivatives, shown in Table 3, were used. L-Prolinamide, which is an effective catalyst for α-selenenylation of aldehydes, displayed poor activity (Table 3, entry 1), whereas the reaction promoted by L-proline took place in a 66% yield after 10 h (entry 2). Reactions employing other organocatalyst, including piperidine, pyrrolidine, and pyrrolidine pentafluorophenylsulfonamide (entries 6–8), were also inefficient. Pyrrolidine trifluoromethanesulfonamide **I** showed the highest catalytic activity (entry 3). In this case, the reaction proceeded rapidly when a 20 mol% catalyst loading was used and a 83% yield was achieved. However, when the loading of **I** was reduced to 5–10 mol%, the reaction rates were significantly lowered.

To demonstrate the scope of this new α-sulfenylation reaction, we probed reactions of various ketones promoted by 20 mol% pyrrolidine trifluoromethanesulfonamide **I**. Generally, high yields (60–88%) were obtained for reactions of cyclic ketones (Table 4, entries 1–3). Unfortunately, α-sulfenylation reactions of acyclic ketone substrates were sluggish and complex product mixtures were produced.

This direct, catalytic α-sulfenylation reaction is not restricted to cyclic ketones since it also is applicable to aldehydes (Table 4, entries 4–11). Variations in the steric demand of aldehydes had only a minor effect on the α-sulfenylation reaction efficiency. Generally, high reaction yields were obtained regardless of the length and degree of branching of the aldehyde chain. Interestingly, in some cases (Table 4, entries 5–7 and 10), bis-addition products were formed in variable, minor amounts (by ^{1}H NMR analysis of the crude product mixtures), however the mono- and bis-products cannot be separated by silica gel column chromatography.

In summary, a pyrrolidine sulfonamide **I** organocatalytic procedure for direct α-sulfenylation reactions of ketones and aldehydes has been developed. This reaction, which produces α-sulfeno-aldehyde and -ketone products, is applicable to a wide range of cyclic ketones and aldehydes. The full scope of this process and its mechanistic intricacies are currently being investigated.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.021.

References and notes

1. (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363–382; (b) Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453–461.
2. (a) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887–4902; (b) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405–4412; (c) Groenewegen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1979**, *20*, 2817–2820; (d) Coates, R. M.; Pigott, H. D.; Ollinger, J. *Tetrahedron Lett.* **1974**, *15*, 3955–3958; (e) Seebach, D.; Teschner, M. *Tetrahedron Lett.* **1973**, *14*, 5113–5116; (f) Seebach, D.; Teschner, M. *Chem. Ber.* **1976**, *109*, 1601–1616; (g) Huang, C.-H.; Liao, K.-S.; De, S. K.; Tsai, Y.-M. *Tetrahedron Lett.* **2002**, *41*, 3911–3914.
3. (a) Asinger, F.; Thiel, M.; Kalzendorf, I. *Justus Liebigs Ann. Chem.* **1957**, *610*, 25–32; (b) Asinger, F.; Schaefer, W.; Triem, H. *Monatsh. Chem.* **1966**, *97*, 1510–1522; (c) Truce, W. E.; Knospe, R. H. *J. Am. Chem. Soc.* **1955**, *77*, 5063–5067.
4. Murai, S.; Kuroki, Y.; Hasegawa, K.; Tsutsumi, S. *Chem. Commun.* **1972**, 946–947.
5. Kuehen, M. E. *J. Org. Chem.* **1963**, *28*, 2124–2128.
6. Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817–2820.
7. Wang, W.; Wang, J.; Li, H. *Chem. Commun.*, submitted for publication.
8. This catalyst showed high catalytic activities for α-aminoxylation and the Mannich-type reactions: (a) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7235–7238; (b) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243–7246.