



α -Phenylselenenylation of aldehydes and ketones with diphenyl diselenide mediated by $\text{KF}/\text{Al}_2\text{O}_3$

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ABSTRACT

The utility of $\text{KF}/\text{Al}_2\text{O}_3$ for the synthesis of α -phenylseleno aldehydes and ketones from the corresponding aldehydes or ketones and diphenyl diselenide has been investigated. Simple stirring of a mixture of aldehyde or ketone and diphenyl diselenide in the presence of $\text{KF}/\text{Al}_2\text{O}_3$ at room temperature selectively produces the corresponding α -phenylseleno aldehyde or ketone in good to excellent yields.

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α -Phenylseleno aldehydes and ketones are important intermediates in organic synthesis¹, which can be converted into the corresponding synthetically useful α,β -unsaturated aldehydes and ketones through selenoxide elimination reactions.² Furthermore, these compounds can undergo oxidation followed by [2,3]-sigmatropic rearrangement to produce allylic alcohols³ and amines.⁴ Various synthetic methods for the preparation of α -phenylseleno aldehydes and ketones have been developed, including direct α -selenenylation of aldehydes or ketones,^{5,2a,c} reaction of electrophilic organoselenium reagents such as PhSeBr or N -(phenylseleno)phthalimide (NPSP) with aldehyde or ketone enolates or enolate derivatives,⁶ and nucleophilic reaction of phenylselenolates with α -halo aldehydes or ketones.⁷ However, most of the reported methods suffer from serious drawbacks such as the necessity of very low temperature (-78°C), low yields, and use of air and moisture sensitive and expensive reagents or poisonous transition metal catalysts. Due to the utility of α -phenylseleno aldehydes and ketones, the development of new, simple, and convenient alternative synthetic methods for their preparation is of considerable importance.

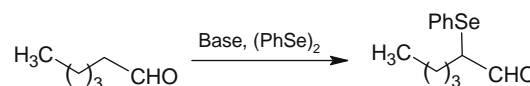
The versatile solid-supported reagent, potassium fluoride loaded on alumina, $\text{KF}/\text{Al}_2\text{O}_3$, which was originally introduced by Ando et al.,⁸ possesses a number of advantages such as simple work-up and isolation of product, increased yield, and shorter reaction times. Moreover, the strong basic nature of $\text{KF}/\text{Al}_2\text{O}_3$

makes it a versatile substitute for organic bases in a variety of reactions such as Suzuki couplings, Sonogashira couplings, Knoevenagel reactions, and N -alkylations of amides and epoxidation reactions.⁹

In continuation of our work on the utility of $\text{KF}/\text{Al}_2\text{O}_3$ in different reactions,¹⁰ we have examined its application in the synthesis of α -phenylseleno aldehydes and ketones by reaction of various aldehydes and ketones with diphenyl diselenide.

In this Letter, we report a very simple, convenient, and high yielding one-pot method for the selective preparation of mono α -phenylseleno aldehydes and ketones, which is mediated by $\text{KF}/\text{Al}_2\text{O}_3$ using stable and commercially available diphenyl diselenide at room temperature under mild conditions.

To optimize the reaction conditions with respect to temperature, solvent, base, and molar ratio of the components, we first conducted the reaction of hexanal and diphenyl diselenide, as a model reaction, under air (Scheme 1). The results are listed in Table 1. When the reaction was performed using other bases (Table 1, entries 1–5), the yields of the desired product were low. In contrast, higher yields of α -phenylseleno-hexanal were obtained when $\text{KF}/\text{Al}_2\text{O}_3$ (38% by weight KF)¹⁰ was used as base. As can be seen from Table 1, the best result was obtained with $\text{KF}/\text{Al}_2\text{O}_3$ in DMF at room temperature (Table 1, entry 9).

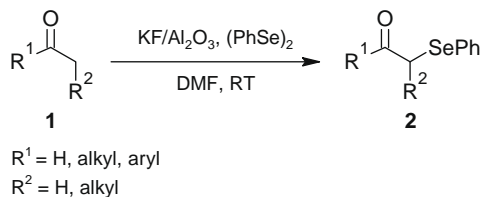


Scheme 1.

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Table 1
Optimization of the α -phenylselenenylation of hexanal

Entry	Base (mmol)	Solvent	Conditions	Yield ^a (%)
1	Basic Al ₂ O ₃ (3)	DMF	25 °C, 2 h	48
2	NaH (3)	DMF	25 °C, 1 h	39
3	Et ₃ N (3)	DMF	25 °C, 24 h	Trace
4	K ₂ CO ₃ (3)	DMF	25 °C, 2 h	43
5	KOH (3)	DMF	25 °C, 1 h	38
6	KF/Al ₂ O ₃ (3)	DMF	25 °C, 20 min	76
7	KF/Al ₂ O ₃ (4)	DMF	25 °C, 20 min	57
8	KF/Al ₂ O ₃ (1.5)	DMF	25 °C, 20 min	63
9	KF/Al ₂ O ₃ (2)	DMF	25 °C, 20 min	79
10	KF/Al ₂ O ₃ (2)	DMF	25 °C, 30 min	77
11	KF/Al ₂ O ₃ (2)	DMF	50 °C, 20 min	30
12	KF/Al ₂ O ₃ (2)	CH ₂ Cl ₂	25 °C, 24 h	0
13	KF/Al ₂ O ₃ (2)	CH ₃ CN	25 °C, 6 h	61
14	KF/Al ₂ O ₃ (2)	THF	25 °C, 24 h	0
15	KF/Al ₂ O ₃ (2)	THF	55 °C, 24 h	0

^a Isolated yield.

In order to probe the scope of the KF/Al₂O₃-mediated α -phenylselenenylation, a variety of aldehydes were treated with diphenyl diselenide (Scheme 2). The results are shown in Table 2.

Table 2
Reaction of aldehydes with diphenyl diselenide mediated by KF/Al₂O₃

Entry	Product ^a	Yield ^b (%)
1		74
2		90
3		79
4		88
5		86
6		76
7		74
8		85

^a References provided for known compounds. Reaction time = 20 min.^b Isolated yield.**Table 3**
Reaction of ketones with diphenyl diselenide mediated by KF/Al₂O₃

Entry	Product ^a	Time (h)	Yield ^b (%)
1		18	95
2		26	75
3		22	88
4		25	65
5		18	88
6		20	80
7		21	92
8		20	89

^a References provided for known compounds.^b Isolated yield.

2. Interestingly, neither condensation adducts nor double α -phenylselenenylated products were detected in the course of these reactions when performed under the optimized reaction conditions.¹¹ The corresponding α -phenylselenenylated aldehydes **2a–h** were obtained in 74–90% yields.

We then examined the α -phenylselenenylation reaction of ketones with diphenyl diselenide (Scheme 2). In our first attempt, 3-pentanone was allowed to react with diphenyl diselenide in the presence of KF/Al₂O₃. Under the previously optimized reaction conditions,¹¹ the corresponding mono α -phenylselenenyl ketone, 2-(phenylselenenyl)pentan-3-one, was obtained in 95% yield after 18 h (**2i**, entry 1, Table 3). Encouraged by this result, we performed the same reaction with various aliphatic and aromatic ketones. The results are presented in Table 3. α -Phenylselenenylated ketones were obtained selectively in 65–95% yields under very mild reaction conditions.

In summary, we have described a straightforward, selective, simple, and efficient KF/Al₂O₃-mediated one-pot procedure for the synthesis of α -phenylseleno aldehydes and ketones under mild reaction conditions with good to excellent yields. Regarding operational simplicity, mild reaction conditions, and cost, this method offers significant advantages over previously reported methods.

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- General procedure for the Kf/Al₂O₃-mediated α -phenylselenenylation of aldehydes and ketones:** To a stirred solution of aldehyde or ketone (0.5 mmol) and Kf/Al₂O₃ (320 mg, 38 wt %, Kf) in DMF (5 mL), diphenyl diselenide (156 mg, 0.5 mmol) was added, and the reaction mixture was stirred at room temperature (25 °C) for the time indicated in Tables 2 and 3. The progress of the reaction was monitored by TLC. After the reaction was complete, the mixture was filtered, and the solid support was washed thoroughly with ethyl acetate. After evaporation of solvents, the crude product was purified by preparative TLC (silica gel, eluent *n*-hexane/EtOAc). Excess diphenyl diselenide was recovered in high purity. Selected data, (**2a**): IR (neat): 1707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.09 (t, *J* = 7.4 Hz, 3H), 1.64–1.77 (m, 1H), 1.82–1.94 (m, 1H), 3.54 (dt, *J* = 7.4, 3.4 Hz, 1H), 7.27–7.33 (m, 3H), 7.51–7.59 (m, 2H), 9.43 (d, *J* = 3.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 12.6, 21.1, 54.7, 125.9, 128.8, 129.2, 135.9, 193.1; (**2b**): IR (neat): 1709 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.38–1.61 (m, 2H), 1.62–1.69 (m, 1H), 1.70–1.87 (m, 1H), 3.62 (dt, *J* = 7.4, 3.7 Hz, 1H), 7.23–7.38 (m, 3H), 7.48–7.55 (m, 2H), 9.39 (d, *J* = 3.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 13.7, 21.2, 29.7, 52.6, 126.0, 128.8, 129.2, 135.8, 193.0; (**2h**): IR (neat): 1704 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.02 (dd, *J* = 14.5, 6.6 Hz, 1H), 3.26 (dd, *J* = 14.5, 8.3 Hz, 1H), 3.91 (ddd, *J* = 8.3, 6.6, 3.0 Hz, 1H), 7.19–7.40 (m, 8H) 7.48–7.53 (m, 2H), 9.50 (d, *J* = 3.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 34.1, 53.5, 125.8, 126.8, 128.6, 129.0, 129.3, 136.1, 138.3, 192.2; (**2k**): IR (neat): 1707 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.32–2.35 (m, 1H), 2.39 (s, 3H), 2.43–2.56 (m, 1H), 2.88–3.00 (m, 2H), 3.09–3.20 (m, 1H), 3.22–3.36 (m, 1H), 3.74–3.81 (m, 1H), 7.22–7.33 (m, 3H), 7.51–7.58 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 37.6, 45.7, 50.1, 55.5, 61.7, 127.9, 129.2, 129.3, 134.0, 205.1; (**2n**): IR (neat): 1702 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.09 (t, *J* = 7.3 Hz, 3H), 1.49 (d, *J* = 7.0, 3H), 2.50 (dq, *J* = 17.3, 7.3 Hz, 1H), 2.79 (dq, *J* = 17.3, 7.3, 1H), 3.82 (q, *J* = 7.0 Hz, 1H), 7.25–7.36 (m, 3H), 7.49–7.56 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 8.4, 16.5, 33.0, 45.1, 127.2, 128.7, 129.1, 135.8, 207.5; (**2p**): IR (neat): 1673 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.67 (d, *J* = 6.8 Hz, 3H), 4.71 (q, *J* = 6.8, 1H), 7.22–7.60 (m, 8H), 7.91 (d, *J* = 7.3, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 17.3, 39.8, 127.0, 128.4, 128.5, 128.9, 129.0, 132.8, 135.9, 136.6, 196.3.