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Expeditious and Chemoselective Synthesis of α-Aryl and α-Alkyl Selenomethylketones via Homologation Chemistry

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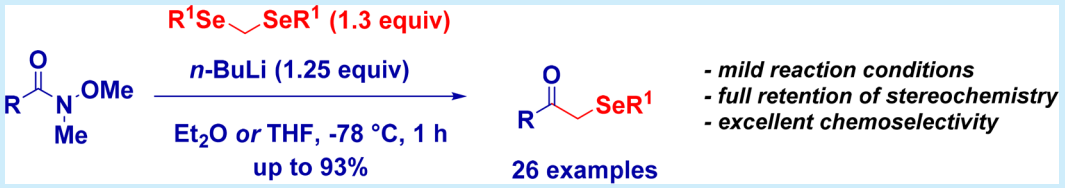
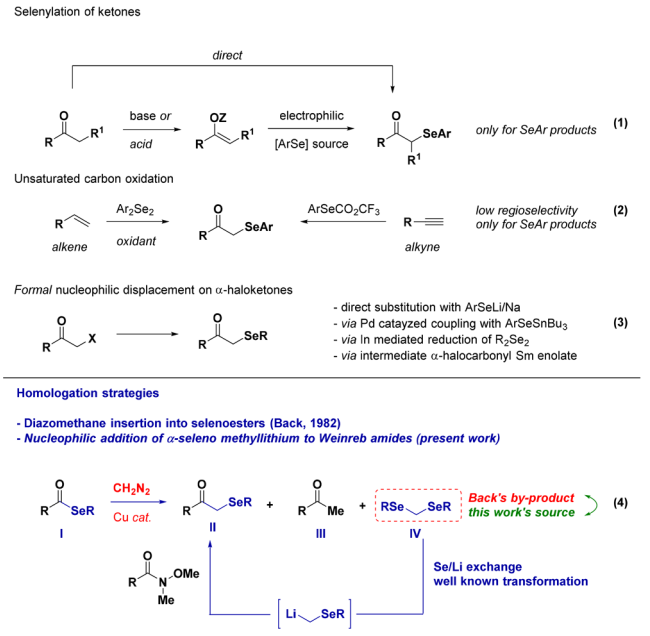
Supporting Information



ABSTRACT: Diselenoacetals, previously considered byproducts in homologation tactics en route to α-selenoketones, are herein found to be excellent starting materials for this purpose. The easy selenium/lithium exchange they undergo affords seleno carbanions which are smoothly added to Weinreb amides to chemoselectively prepare α-aryl- and α-alkyl seleno methylketones through a single chemical operation. No racemization events are observed in the presence of optically pure starting materials.

The unique physical−chemical properties of selenium make the corresponding organometallic compounds formidable intermediates in modern chemistry.[1] The ideal balance between reactivity and selectivity observed through their judicious employment accounts for a prominent position in the design of chemo-, regio-, and stereocontrolled reactions.[2] In this context, the introduction of selenium (via electrophilic, nucleophilic, or radical chemistry) into organic arrays becomes crucial in order to exploit this synthetic potential.[3] Within the broad variety of organoselenium compounds, substituted α-seleno methylketones[1a,4] represent particularly versatile manifolds as documented in the seminal studies by Sharpless,[5] Reich,[6] and Clive.[7] In fact, the extremely mild *syn* elimination of selenoxides they undergo constitutes currently an established tool for obtaining α,β-unsaturated carbonyls of particular interest, *inter alia*, for natural products synthesis.[2a−d,8] From a conceptual point of view, the available preparative strategies can be included into the following main categories (Scheme 1): (1) electrophilic selenylation of ketones direct or via the corresponding enolates and enols (Scheme 1, eq 1);[5b,6a,9] (2) oxidation of olefins[10] or acetylenes[11] in the presence of electrophilic selenium sources (Scheme 1, eq 2); (3) formal substitution on α-haloketones with nucleophilic selenium species such as RSeLi/Na[6b] or generated via Pd-,[12] Sm-,[13] and In-mediated[14] processes (Scheme 1, eq 3). Although they represent useful platforms toward *cyclic* α-seleno ketones, the preparation of *acyclic* analogues and the synthesis of *α-alkyl* seleno ketones have been only partially addressed. Additionally, low regioselectivities, nonoptimal chemical yields, and a well-defined requirement for the nature of the selenylating reagent further narrow the applicability of these methods. In this context, the homologation of seleno esters[15] **I** with diazomethane, via its insertion into the acyl-selenium linkage under

Scheme 1. α-Selenomethyl Ketones: State-of-the-Art



Cu catalysis, first documented by Back in 1982, constitutes one of the very few syntheses of α-substituted seleno methylketones **II** adaptable to both *alkyl* and *aryl* functionalities (Scheme 1, eq 4).[16] However, such an advantage was counterbalanced by rather limited chemical yields and by the formation of

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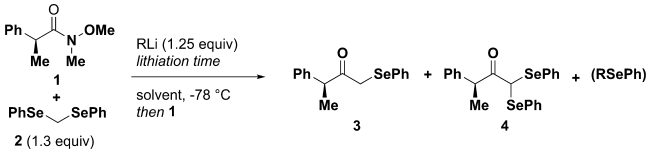
byproducts, consisting of methylketone **III** and selenoacetal **IV**, in considerable amounts. In particular, the generation of the diselenoacetal, for instance, obtainable in high yield through simpler techniques,[17] was quite intriguing for us, as, in principle, it could act as a convenient source of a lithium substituted α-methyl seleno carbanion ($LiCH_2SeR$) via the well-suited selenium−lithium exchange.[18] Moreover, our previous experience in preparing α-substituted ketones through the acyl nucleophilic displacement of α-functionalized methyllithium derivatives[19] to Weinreb amides[20] further spurred us to undertake the study, and herein we report a straightforward and versatile method to synthesize α-*aryl*seleno- and α-*alkyl*seleno-methylketones through a single synthetic operation. We anticipate the byproduct diselenoacetal formed under Back's condition represents the manifold for the crucial α-seleno methyl carbanion required in our tactic.

Our investigations commenced by selecting the enantiopure Weinreb amide **1** as a valuable acylating agent and the aromatic diselenoacetal **2** as the putative precursor for the key α-seleno methyl lithium carbanion (Table 1). According to the accepted

Table 1. Model Reaction: Optimization[a]



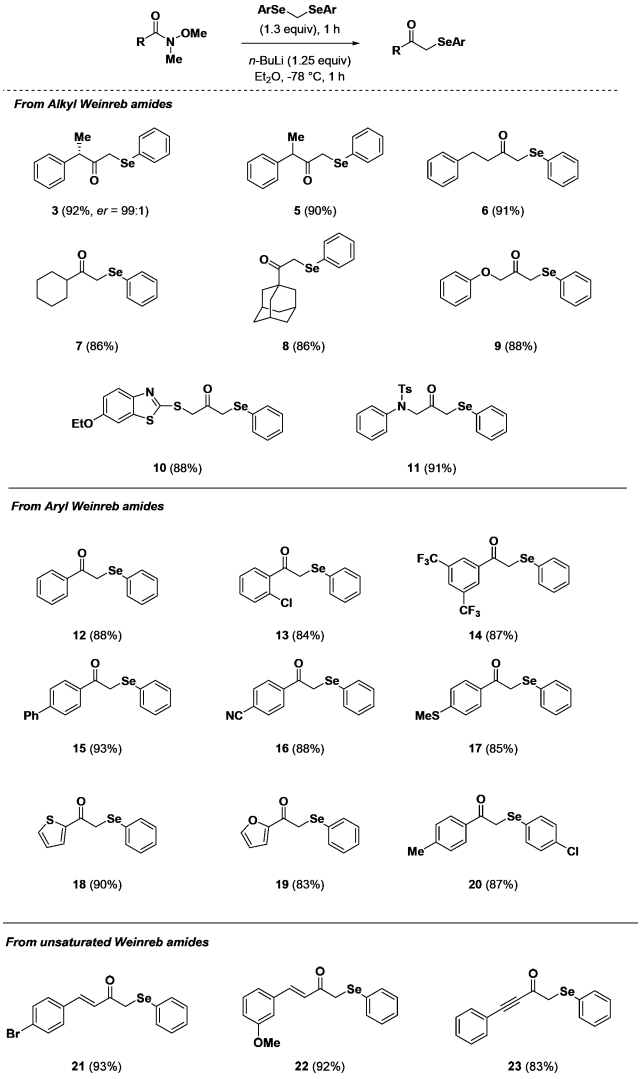
entry	solvent	Lithiation time (min)	ratio 3/4	yield of 3 (%)[a]	er of 3
1	THF	10	97:3	78	96:4
2	THF	5	14:86	–[b]	–
3[c]	THF	10	27:73	–	–
4	Et_2O	5	93:7	86	98:2
5	Et_2O	10	95:5	88	98:2
6	Et_2O	30	97:3	89	99:1
7	Et_2O	60	>99:1	92	99:1
8	MTHF	60	94:6	84	95:5
9	toluene	60	92:8	81	99:1
10[d]	Et_2O	60	26:74	17	–
11[e]	Et_2O	60	21:79	13	–

[a]Unless otherwise stated *n*-BuLi (1.6 M in hexanes) was used as a lithiating agent, and yields refer to isolated ones. [b]Compound **4** was obtained in 61% isolated yield. [c]TMEDA (1.25 equiv) was added. An overall conversion of 22% was observed by ^1H NMR. [d]*s*-BuLi (1.25 equiv) was used: **4** (61% isolated yield). [e]*t*-BuLi (1.25 equiv) was used: **4** (67% isolated yield).

mechanism for the Se/Li exchange,[18c] the formation of the carbanion would deliver 1 equiv of selenoether PhSeR, thus allowing the estimation of the exchange rate. Generating the nucleophile with *n*-BuLi in THF cleanly provided the desired α-selenomethyl ketone **3** after a lithiation time of 10 min with good enantiopurity (Table 1, entry 1). Some points merit a mention: (a) decreasing the lithiation time to 5 min dramatically affects the yield of **3**, the bis-seleno ketone **4**, originated from the simple deprotonation of **2**, being the major product (Table 1, entry 2); (b) analogously, the addition of TMEDA favors the deprotonation rather than the desired Se/Li exchange (Table 1, entry 3). By using Et_2O as the solvent, chemoselectivity was fully shifted toward our goal (Table 1, entries 4−6), and after a lithiation time of 60 min, it was practically complete and enantiopure (*er* > 99:1) (Table 1, entry 7). It is worth mentioning that the full transfer of the stereochemical information of the Weinreb amide during the process indicated almost no racemization takes place despite the strong basicity of the medium. Attempts to employ different solvents [2-methyltetrahydrofuran (MTHF) or toluene] (Table 1, entries 8−9) diminished both the chemical yield and optical purity of **3**. More sterically hindered *s*-BuLi and *t*-BuLi acted almost exclusively as a base, thus resulting in the prevalent formation of the deprotonation derived product **4** (Table 1, entries 10−11). The absence of noticeable enolization phenomena under our reaction conditions should be highlighted, despite the use of strongly basic α-phenylseleno methyllithium.

With the optimized conditions in hand, we then explored the scope of the reaction (Scheme 2). Alkyl Weinreb amides are

Scheme 2. Scope of the Reaction: Synthesis of α-Arylseleno Methyl Ketones



excellent substrates for the transformation, providing the corresponding α-phenylseleno methylketones **3**−**11** in average yields of >86%. Notably, the protocol is not influenced by the sterical hindrance of the acylic moiety as deduced in the case of the adamantyl derivative **8**. Interestingly, starting from α′-heteroatom substituted Weinreb amides, it is possible to prepare previously unknown α′-oxo-, α′-thio-, and α′-amino- α-

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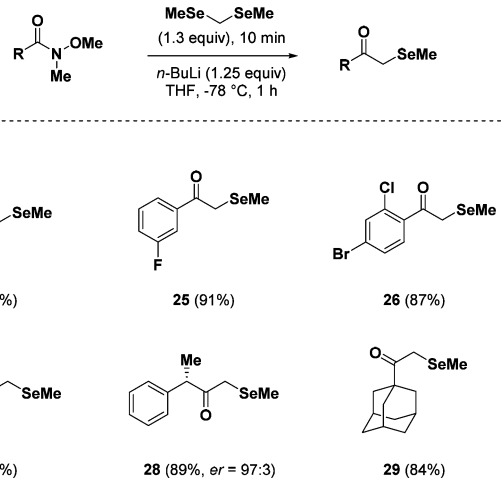
phenylseleno acetones **9**–**11** through a unique operation. The protocol works well also in the case of aryl Weinreb amides **12**–**20**. Accordingly, substitution across the aryl nuclei is permitted at the *ortho*, *meta*, and *para* position with different functionalities such as chloro **13**, trifluoromethyl **14**, and thioether **17** as well as the use of heteroaromatic acylating agents **18**–**19**. The formed carbanion displays excellent chemoselectivity toward the Weinreb amide even in the case of the simultaneous presence of an additional electrophilic group as a nitrile **16**. The technique is amenable for introducing a functionalized arylseleno (p-ClC_6H_4Se, **20**) methyl carbanion, thus expanding the versatility of the method. Sensitive substrates such us α,β-unsaturated Weinreb amides react with excellent 1,2-selectivity, thus giving the corresponding phenylseleno ketones **21**–**22** in high yields. These results clearly highlight the potentiality of our method because of the observed Michael-type addition on similar α,β-unsaturated analogues.[18a] Notably, a potentially exchangeable bromine, which in analogous systems could interfere with the selenium–lithium exchange,[4b] did not affect the chemoselectivity (**21**). Moreover, an alkyne Weinreb amide undergoes the transformation with unchanged efficiency (**23**).

With the aim to develop a versatile method suitable also for α-*alkyl* seleno methylketones and cognizant of the more difficult Se/Li exchange on bis(*alkyl*seleno)acetals,[4a,18a] we were not surprised to observe only traces of the desired compound **24** by applying the above established conditions [$(RSe)_2CH_2$ (1.3 equiv), *n*-BuLi (1.25 equiv), Et_2O, −78 °C)]. Pleasingly, the simple switching to THF, *coeteris paribus*, allowed 95% conversion to be obtained (as evidenced by ^1H NMR on the reaction crude), which finally resulted in an excellent 90% isolated yield (Scheme 3). The reaction shows a

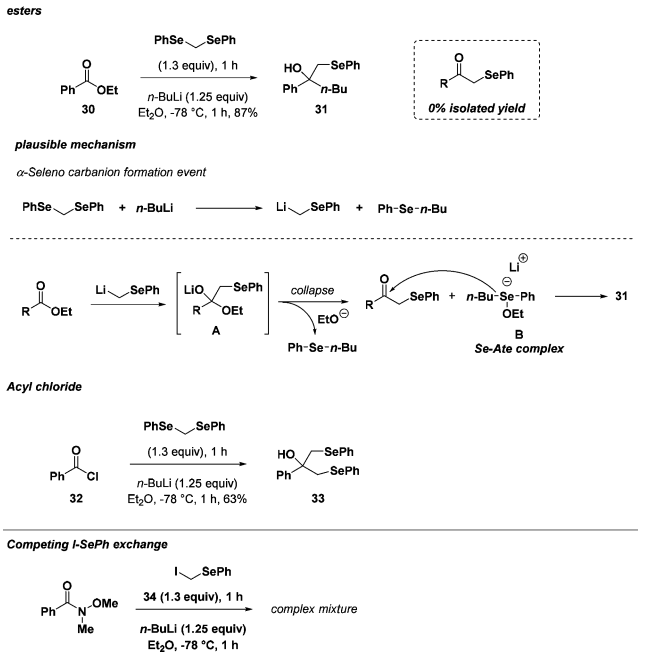
Scheme 3. Synthesis of α-Methylseleno Methyl Ketones



similar broad scope, thus enabling the addition–elimination sequence of the methylseleno methyl lithium carbanion to Weinreb amides, finally leading to the targeted seleno methylketones **24**–**29**. The stereochemical information featured in the starting material could be fully transferred to the final compound **28**. Again, the presence of an exchangeable halogen (**26**) or a bulky substituent (adamantyl, **29**) is irrelevant in determining both selectivity and efficiency.

In order to acquire full insights into the transformation and because of the limited studies available on the acylation, via nucleophilic substitution, of α-seleno carbanions,[4a,18c] the reactivity of different acylating agents (ester and chloride) was separately investigated (Scheme 4). Accordingly, by

Scheme 4. Use of Different Acylating Agents or Seleno Sources



reacting ester **30** under the classical conditions, carbinol **31** surprisingly resulted as the unique reaction product in 87% yield. Presumably, the collapse of the tetrahedral intermediate **A** generated upon the addition of $LiCH_2SePh$ to the ester delivers an alkoxy residue[21] which is intercepted by PhSe-*n*-Bu (byproduct of the seleno carbanion formation event), giving a selenium–*ate* complex **B**. Subsequently, the latter acts as a latent source of *n*-Bu carbanion, which in turn attacks the putative α-selenoketone, finally giving **31**. The use of a chloride **32** as the acylating agent yielded the diseleno-carbinol **33**, in agreement with the commonly accepted overaddition of organometallics to these electrophiles. On the other hand, attempting the generation of $LiCH_2SePh$ via iodine/lithium exchange on iodomethyl phenylselenoether **34** gave a complex reaction mixture, further indicating the Se/Li exchange on diselenoacetal as the ideal method to prepare such a carbanion. These experiments confirm the usefulness of the combination of Weinreb amides and diselenoacetals for preparing α-selenoketones under lithiation conditions.

In conclusion, we have developed an expeditious access to aryl and alkyl selenomethyl ketones via the highly chemoselective nucleophilic addition of α-selenomethyl lithium carbanions to variously functionalized Weinreb amides. The present method documents the effectiveness of generating the requested nucleophilic seleno carbanion from a diselenoacetal which in the previously reported diazomethane homologation strategy was considered a byproduct of the reaction. Key features of the transformation are (1) uniformly high yields and full retention of the sterical information contained in the starting materials for both processes (α-arylseleno and α-alkylseleno) and (2) excellent chemoselectivity in the presence of functionalities sensitive to lithium organometallics including halogen, α,β-unsaturated systems.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedure, NMR spectra, HPLC traces and analytical data for all the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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