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Radical Cascade Reaction of Aryl Alkynoates at Room Temperature: Synthesis of Fully Substituted α,β-Unsaturated Acids with Chalcogen Functionality

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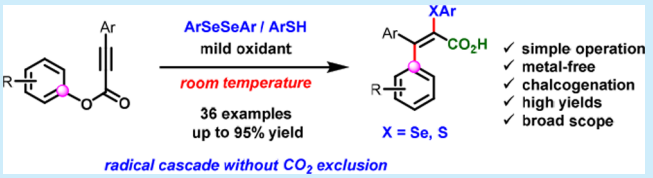
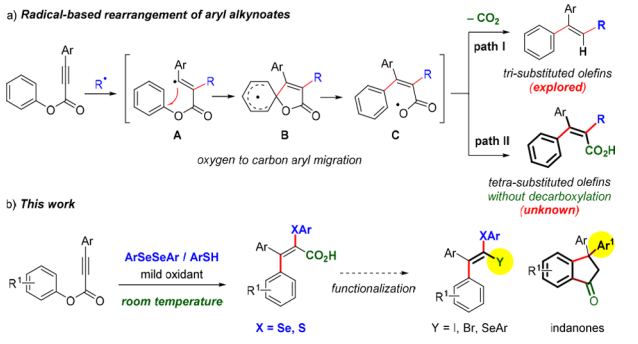
Supporting Information

ABSTRACT: A radical-based cascade reaction has been devised for oxidative difunctionalization of aryl alkynoates at room temperature to access stereodefined fully substituted α,β-unsaturated acids bearing a chalcogen functionality in high yields (up to 95%). The protocol is operationally simple, metal-free, scalable, and suppresses the usual CO_2 exclusion phenomenon. The utility of this method was showcased in the synthesis of vinyl halides, vinyl selenides, and 3,3-disubstituted indanones.



Aryl alkynoates are reliable coupling partners in atom transfer radical cascade reactions, and various molecular frameworks have been constructed taking advantage of the radical acceptor property of the activated alkyne functionality.[1−3] Recently, this radical cascade has been advanced for 1,4-aryl migration that resembles Smiles rearrangement (see Scheme 1a).[4,5] All of these

Scheme 1. Radical-Based Rearrangement of Aryl Alkynoates and Synthesis of Substituted Olefins and α,β-unsaturated acids



radical-based rearrangements were primarily performed at elevated temperature, and only trisubstituted olefins were obtained after the decarboxylation process (Path I, Scheme 1a).[6] We envisioned that the decarboxylation step would be interrupted if the radical-based Smiles rearrangement process can be executed under mild conditions. If successful, the protocol will not only disclose a new mode of radical cascade of aryl alkynoates, but also deliver unsymmetrically tetrasubstituted acyclic olefins embracing carboxylic acid as one of the substituents (Path II, Scheme 1a). Note that the presence of a carboxylate functionality is advantageous, since it can be easily transformed to a broad range of functional groups, indicating wide application prospects in chemical production. Furthermore, synthesis of tetrasubstituted α,β-unsaturated acids decorated with four different substituents is highly challenging, because of difficulties in controlling the stereoselectivity. The situation becomes particularly more daunting where acyclic systems with sensitive functional groups and heteroatom substitutions are concerned. In our approach, an exquisite stereo control is expected, as both radical addition and 1,4-aryl migration steps would proceed in a highly regioselective fashion.

Molecules comprising C−Se and C−S bonds, or organochalcogenides, represent an important structural motif in bioactive molecules.[7] They are pivotal building blocks in synthetic organic chemistry and have found extensive applications in functional materials.[8] Consequently, synthetic methods that efficiently install a chalcogen functionality into organic molecules are highly desirable. With our continuous interest in organochalcogenide chemistry,[9] herein, we report an unprecedented metal-free atom transfer radical cascade reaction for difunctionalization of aryl alkynoates with diselenides and thiols en route to fully susbtituted α,β-unsaturated acids embracing a chalcogen functionality at room temperature (see Scheme 1b). The synthetic utility of this protocol was further highlighted through the production of vinyl selenides, vinylhalides, and 3,3-disubstituted indanones.

We commenced our investigation with the reaction of aryl alkynoate **1a** with diphenyldiselenides **2a**. Gratifyingly, when the mixture of **1a** and **2a** was stirred in the presence of *tert*-butyl hydroperoxide (TBHP) as the oxidant at room temperature in acetonitrile solvent, selenium-radical-induced cascade rearrangement with 1,4-aryl migration from the oxygen center to the carbon center occurred smoothly to deliver desired tetrasubstituted alkene **3a** in 95% isolated yield (Table 1, entry 1). The compound **3a** was crystallized, and X-ray analysis unambiguously established the structure of the acid. It also supports the

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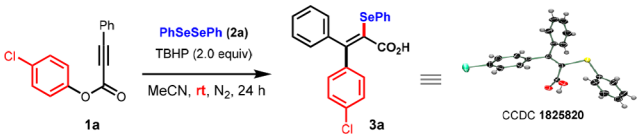
Table 1. Optimization of Reaction Conditions[a]



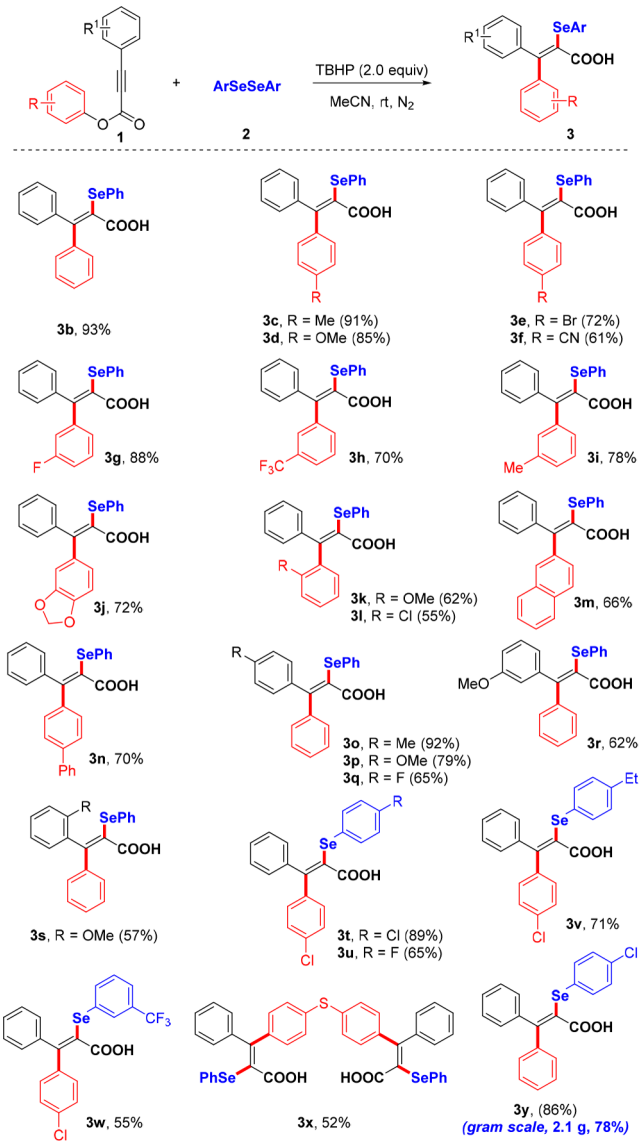
entry	deviation from optimal conditions	yield (%)
1	**none**	**95**
2	DCE instead of MeCN	68
3	THF instead of MeCN	44
4	toluene instead of MeCN	56
5	DMSO instead of MeCN	trace
6	DMF instead of MeCN	27
7	MeOH instead of MeCN	32
8	DCP instead of TBHP	15
9	DTBP instead of TBHP	trace
10	H_2O_2 instead of TBHP	trace
11	under air atmosphere	77
12	1.5 equiv of TBHP was used	75
13	1.0 equiv of TBHP was used	48
14	without TBHP	0
15	1.5 equiv of PhSeSePh was used	81
16	1.0 equiv of PhSeSePh was used	54

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), TBHP in decane solution (0.4 mmol), MeCN (1.5 mL), room temperature (rt), 24 h. Isolated yields. TBHP = *tert*-butyl hydrogen peroxide; DCP = dicumyl peroxide; DTBP = di-*tert*-butyl peroxide.

regioselective outcome, which is consistent with the postulated reaction mechanism depicted in Scheme 1. Screening of other solvents, such as tetrahydrofuran (THF), methyl alcohol (MeOH), dimethyl sulfoxide (DMSO), and dimethyl formamide (DMF), instead of CH_3CN, gave inferior results (Table 1, entries 2−7). The reaction was very sluggish when oxidants such as dicumyl peroxide (DCP), di-*tert*-butyl peroxide (DTBP), and hydrogen peroxide (H_2O_2) were tested, and the starting material **1a** was recovered for all these cases (Table 1, entries 8−10). The yield was also reduced from 95% to 77%, when the reaction was carried out in open air (Table 1, entry 11). The output was highly governed by *tert*-butyl hydrogen peroxide (TBHP) loading; the reaction yields gradually decreased with the lowering of the amount of TBHP and was completely shut down in the absence of TBHP (Table 1, entries 12−14). Examination of the amount of diselenide **2a** in the reaction revealed that the yield dropped significantly with the reduction of diselenide loading (Table 1, entries 15 and 16).

With the optimized conditions in hand, the scope of the cascade process was explored (see Scheme 2). The reaction was quite general for a wide range of aryl alkynoates having electron-donating substituents such as methyl (**3c** and **3i**), alkoxy (**3d** and **3k**) and electron-withdrawing substituents, such as bromo (**3e**), cyano (**3f**), fluoro (**3g**), and trifluoromethyl (**3h**) at the *para*- and *meta*-positions of the *O*-aryl ring, delivering fully substituted *α,β*-unsaturated acids in high yields (61%−93%). Satisfyingly, *ortho*-substituted hindered aryl alkynoates also produced desired products **3k** and **3l** in 62% and 55% yields, respectively. Naphthyl and biphenyl substitutions did not hamper the radical cascade process to offer **3m** and **3n** in good yields. Variation in the alkyne aryl substituent was also considered; *para* (**3o**−**3q**), *meta* (**3r**), and *ortho* (**3s**) substituted alkynoates provided the desired products in good yields (57%−92%).

Scheme 2. Substrate Scope for Radical Cascade Selenylation of Aryl Alkynoates[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), TBHP in decane solution (0.4 mmol), MeCN (1.5 mL), rt, 24 h. Yields of isolated products are given.

The reaction efficiency of different diselenides was also investigated (see Scheme 2). Diaryl diselenides with different halogens (**3t** and **3u**), ethyl (**3v**), and trifluoromethyl (**3w**) substituents furnished products in moderate to high yields (55%−89%). Interestingly, when thio-bis(4,1-phenylene)bis(3-phenylpropiolate) (**1x**) was exposed to the standard reaction conditions, a 2-fold cascade rearrangement occurred efficiently and the olefin **3x** with a thio ether link was isolated in 52% yield. The scaleup was also compatible and a gram-scale reaction of alkynoate **1y** rendered the desired product **3y** in 78% yield (see Scheme 2).

The versatility of the protocol was further tested using different organochalcogenides. While the exposure of PhSSPh to aryl alkynoate **1a** under standard reaction conditions was unable to deliver sulfur-substituted acid **5a**, the sulfenyl radical-based cascade rearrangement with stipulated regioselectivity occurred smoothly with simple thiophenol under the same conditions

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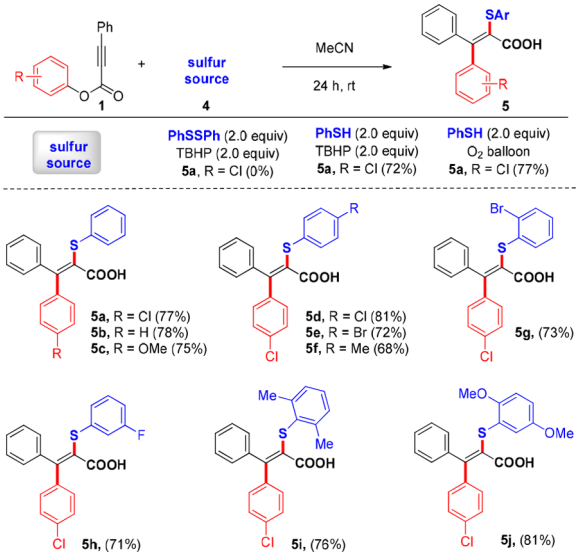
(Scheme 3). Further optimization revealed that the utilization of TBHP for the installation of sulfenyl functionality was not

Scheme 3. Substrate Scope for Radical Cascade Sulfenylation of Aryl Alkynoates[a]

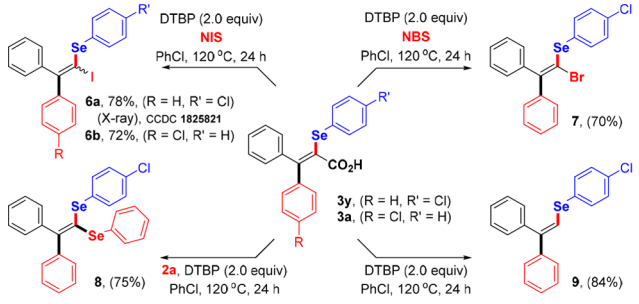


[a]Reaction conditions: **1** (0.2 mmol), **4** (0.4 mmol), O_2 balloon, MeCN (1.5 mL), rt, 24 h. Yields of isolated products are given.

mandatory and the reaction was fruitful in the presence of molecular oxygen only, producing **5a** in 77% yield (Scheme 3). Irrespective of the substitution patterns, both electron-rich and electron-deficient aryl thiols delivered the desired sulfur-substituted α,β-unsaturated acids **5a**–**5j** in uniformly high yields (68%–81%; see Scheme 3).

The formed tetrasubstituted alkenes with a carboxylate functional group demonstrated versatile reactivity. Treatment of **3y** with NIS or NBS in the presence of DTBP at 120 °C triggered a decarboxylative cross-coupling process to give selenylated vinyl iodide (**6a**) and bromide (**7**), respectively (see Scheme 4). With the product **3a** having different β-aryl

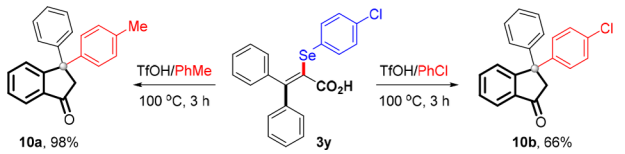
Scheme 4. Post-functionalization of the Selenylated Products Post-functionalization of the Selenylated Product



groups, iodinated compound **6b** was isolated in a 1:1 mixture of regioisomers.[6g] The halogen functionalities provide a good synthetic handle for further synthetic modifications. When the decarboxylative cross-coupling was performed with diselenide **2a**, geminal diselenoether **8** was formed in 75% yield. In the absence of any cross-coupling partner, vinyl selenide **9** was isolated in 84% yield (Scheme 4).[10]

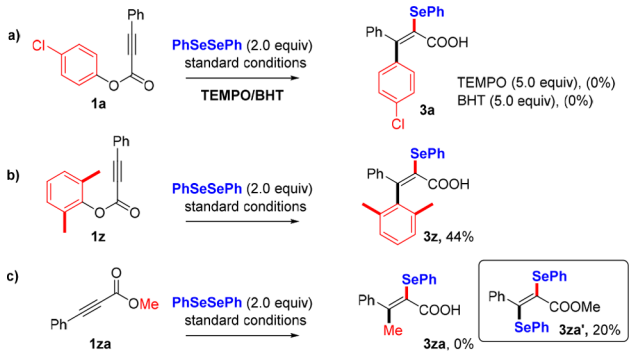
The synthetic utility of the protocol was further highlighted through the synthesis of substituted indanones, which are important scaffolds. Accordingly, product **3y** was treated with triflic acid at 100 °C in toluene and chlorobenzene solvents separately, furnishing 3,3-disubstituted indanones **10a** and **10b**, in 98% and 66% yields, respectively (see Scheme 5). Here, an intramolecular cyclization involving a 1,4-addition reaction of solvent molecules occurred (details are included in the Supporting Information (page S6)).

Scheme 5. Synthesis of 3,3-Disubstituted Indanones



In order to gain mechanistic insight, various control experiments were performed (see Scheme 6). The reaction was

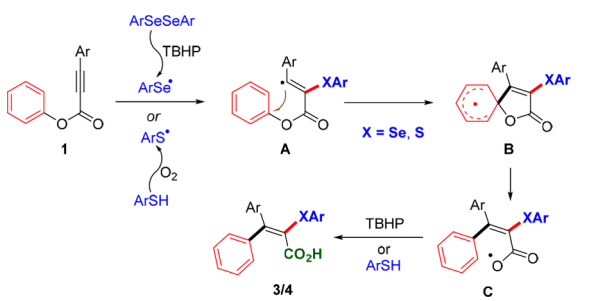
Scheme 6. Control Experiments



unproductive in the presence of radical scavengers such as TEMPO and butylated hydroxytoluene (BHT), suggesting the involvement of a radical species in the reaction pathway (Scheme 6a). The reaction of aryl alkynoate **1z** having a bis *ortho*-substituted aromatic ring gave the desired product in 44% yield, refuting classical neighboring group participation process (Scheme 6b).[6a] Also, when **1za** was subjected to the standard reaction conditions, no 1,4-migration product **3za** was observed; instead, a diselenylated product **3za′** was isolated in 20% yield (see Scheme 6c). All these findings favor a *spiro*-cyclic intermediate[6b] for the radical-based cascade process.

Based on these findings and previous reports,[6] a plausible reaction mechanism is outlined in Scheme 7. The aryl chalogen radical generated upon treatement with TBHP or O_2 reacts with

Scheme 7. Plausible Reaction Mechanism



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alkynyl bond of **1** and produces the vinyl radical **A**. The intermediate **A** undergoes an intramolecular radical *ipso*-cyclization to afford **B**, which, upon aryl migration from the oxygen center to the carbon center, gives the carboxyl radical **C**. Finally, the carboxyl radical **C** extracts a hydrogen radical from the TBHP or ArSH[6c] to deliver the desired products **3**/**4**.

In conclusion, we have developed a metal-free radical-based cascade reaction of aryl alkynoates at room temperature to provide a series of unsymmetrically tetrasubstituted α,β-unsaturated acids with a chalcogen functionality in good to excellent yields. The process involves the construction of C−Se/S, C−C bonds and the cleavage of a C−O bond in a single operation and overcomes the well-known CO_2 exclusion phenomenon. The protocol is operationally simple, scalable, and displays a broad substrate scope. The products were also efficiently utilized for a novel decarboxylative radical cross-coupling to access vinyl halides, vinyl selenides, and geminal diselenoethers, and in the synthesis of 3,3-diaryl indanones. Control experiments support a radical mechanism for this process. Further applications of this strategy in other carbon−heteroatom bond forming reactions are currently being pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01474.

Complete experimental details, characterization data for the prepared compounds (PDF)

Accession Codes

CCDC 1825820 and 1825821 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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