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Selenium-Catalyzed C(sp^3)–H Acyloxylation: Application in the Expedient Synthesis of Isobenzofuranones

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Dedicated to Professor Barry M. Trost

Abstract: Oxidative Se-catalyzed C(sp^3)–H bond acyloxylation has been used to construct a diverse array of isobenzofuranones from simple *ortho*-allyl benzoic acid derivatives. The synthetic procedure employs mild reaction conditions and gives high chemoselectivity enabled by an inexpensive organodiselane catalyst. The presented approach offers a new synthetic pathway toward the core structures of phthalide natural products.

The direct and controlled installation of oxygen and nitrogen functionalities into hydrocarbon architectures constitutes a powerful yet extraordinarily challenging strategy in contemporary synthetic chemistry.[1] Due to the omnipresence of carbon–hydrogen bonds in organic molecules with low oxidation states, the chemo- and regioselective functionalization of a single C–H entity is extremely difficult.[2] However, the discriminative and forthright manipulation of a particular bond class can significantly streamline the overall synthetic scheme of a given target molecule.[2] Consequently, the continuous development of new reaction concepts and the advancement of efficient and economical protocols to overcome these intricacies are of paramount importance to numerous scientific disciplines, such as medicinal chemistry, material sciences,[3] and natural product synthesis.[1,2] With regard to allylic C(sp^3)–H oxygenation reactions, numerous elegant transition metal-catalyzed methods have been devised throughout the last three decades.[3,4] In 2004, White and co-workers reported an early example of a Pd-catalyzed allylic acetoxylation reaction of terminal alkenes with switchable regioselectivity.[6] The formation of linear products was predominant when $Pd(OAc)_2$ and benzoquinone as the terminal oxidant were used. In contrast, use of a bis-sulfoxide-ligated Pd^{II} catalyst furnished the corresponding branched products with moderate to excellent selectivity.[6,7] Stahl and co-workers recently described the use of $Pd(OAc)_2$ as a precatalyst and 4,5-diazafluorenone as an ancillary ligand to enable the conversion of terminal olefins into linear allylic acetates using molecular O_2 as an oxidant. In addition to palladium complexes, other promoters, such as copper salts[4c,8] or iodine compounds,[9] proved very efficient in the allylic acyloxylation of alkenes. Early reports on asymmetric variants of such transformations date back to the work of Denney and co-workers in 1965.[10] A conceptually cognate yet mechanistically dissimilar, selenium-mediated protocol for the direct insertion of oxygen substituents into allylic carbon-hydrogen bonds is the Riley-Guillemonat oxidation.[11] Due to the mild reaction conditions and the high functional group tolerance, this selenium dioxide-based allylic hydroxylation has experienced widespread application in the total synthesis of biologically active natural products.[12] Although catalytic versions of this reaction have been described,[11d] the corresponding direct acyloxylation has, to the best of our knowledge, remained elusive until this day.

We previously reported the first examples of allylic and C(sp^2)–H aminations of unactivated linear olefins and cycloalkenes, respectively, facilitated by simple, redox-active diaryldiselane catalysts.[13] On the basis of these initial studies, we became interested in further exploring the potential and utility of selenium-catalyzed oxidations in the context of the cognate allylic acyloxylation using *N*-fluorobenzenesulfonimide (NFSI) as the terminal oxidant (Scheme 1).[14] This method design is particularly challenging because of two critical factors—namely chemoselectivity (acyloxylation vs. amination) and regioselectivity (allylic vs. vinylic position of the carboxylate group) in the course of the carbon–oxygen bond-forming event. To address these issues, we decided to investigate the intramolecular benzoyloxylation of tethered alkene moieties to form isobenzofuranone scaffolds.[15] Such a strategy does not only provide new insights into selenium catalysis but it also offers a novel, step-economic avenue towards core-structures of phthalide natural products (Scheme 1).[16] Consequently, we present herein the first Se-catalyzed synthesis of isobenzofuranones from *ortho*-allyl benzoic acid derivatives through C(sp^3)–H oxidation.

At the outset of our investigations, we had the intention to assemble isobenzofuranones of type **2** by C(sp^2)–H acyloxylation [Equation (1)]. Thus, we used (*E*)-2-(prop-1-en-1-yl)benzoic acid (**1a**) as a representative substrate to explore the feasibility of this approach. When compound **1a** was treated with NFSI (1 equiv) and $(PhSe)_2$ (5 mol%) in dichloromethane at room temperature, we observed the formation of a 1.3:1 mixture of isobenzofuranone **2a** and isocoumarine **3a**, with a total yield of 61%.[17]

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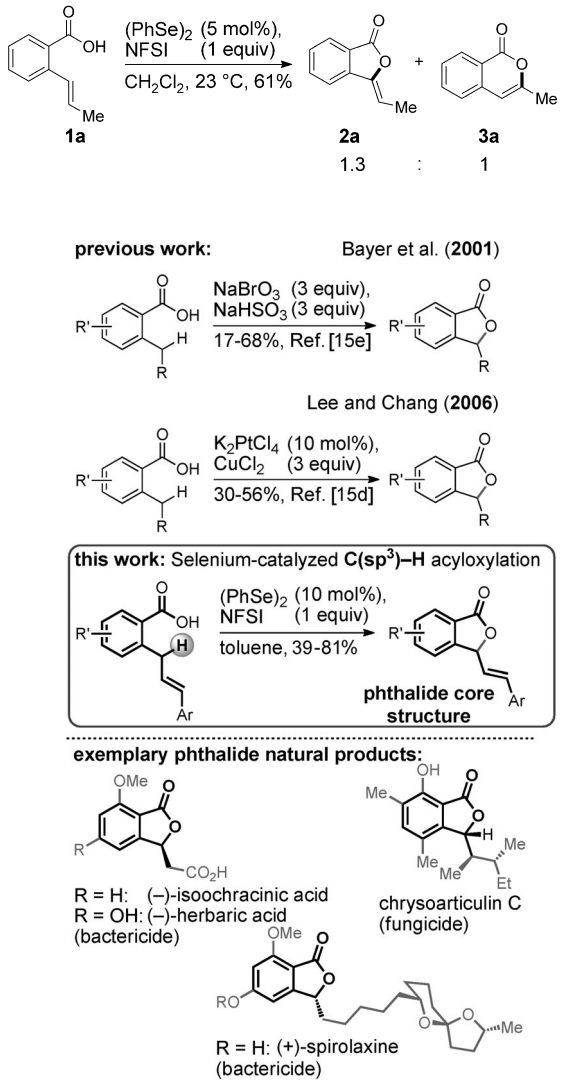
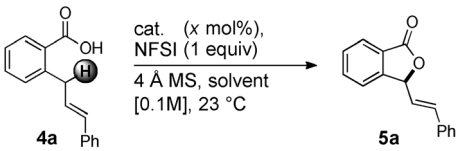


Scheme 1. Exemplary strategies for the construction of isobenzofuranones via C(sp^3)–H oxidation and representative phthalide natural products.

Despite thorough screening for other solvents, catalysts, and reaction temperatures, none of the tested reaction conditions changed the selectivity in favor of the desired isomer **2a**. Since the kinetic preference for 5-*exo*-trig versus 6-*endo*-trig cyclization turned out to be marginal in the case of vinylated substrates **1**, we subsequently decided to use homologous 2-cinnamylbenzoic acid (**4a**) as an alternative in order to selectively obtain the corresponding 6-*exo*-trig cyclization product. In contrast to our expectations, treatment of compound **4a** with NFSI (1 equiv) and $(PhSe)_2$ (5 mol%) in toluene at room temperature cleanly led to the formation of (*E*)-3-styrylisobenzofuranone (**5a**) in a yield of 31% (Table 1, entry 1).[18]

To our knowledge, this transformation constitutes the first example of a diselane-catalyzed intramolecular C(sp^3)–H acyloxylation of a simple allylic entity. Encouraged by this initial result, we sought to optimize this process. Increasing the amount of $(PhSe)_2$ from 5 to 10 mol% resulted in an increased yield of 69% (Table 1, entry 2). Further increasing the catalyst loading to 20 mol% did not have any additional benign effects

Table 1. Optimization of the selenium-catalyzed C(sp^3)–H acyloxylation.



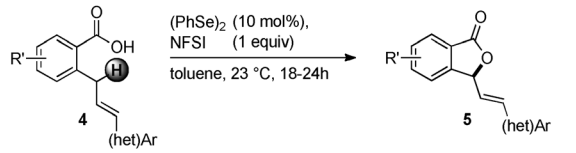
Entry	Catalyst	Catalyst loading [mol%]	Solvent	Yield [%][a]
1	$(PhSe)_2$	5	toluene	31
2[b]	**$(PhSe)_2$**	**10**	**toluene**	**69**
3	$(PhSe)_2$	10	Et_2O	60
4	$(PhSe)_2$	10	THF	49
5	$(PhSe)_2$	10	1,4-dioxane	46
6	$(PhSe)_2$	10	DMSO	nc
7	$(PhSe)_2$	10	DMF	40
8	$(PhSe)_2$	10	$MeNO_2$	34
9	$(PhSe)_2$	10	CH_2Cl_2	27
10	$(PhSe)_2$	10	hexane	23
11	$(BnSe)_2$	10	toluene	5
12	-	0	toluene	4
13	$[Pd(dppf)Cl_2]$	5	toluene	0
14	$[Pd(TFP)_2Cl_2]$	5	toluene	0

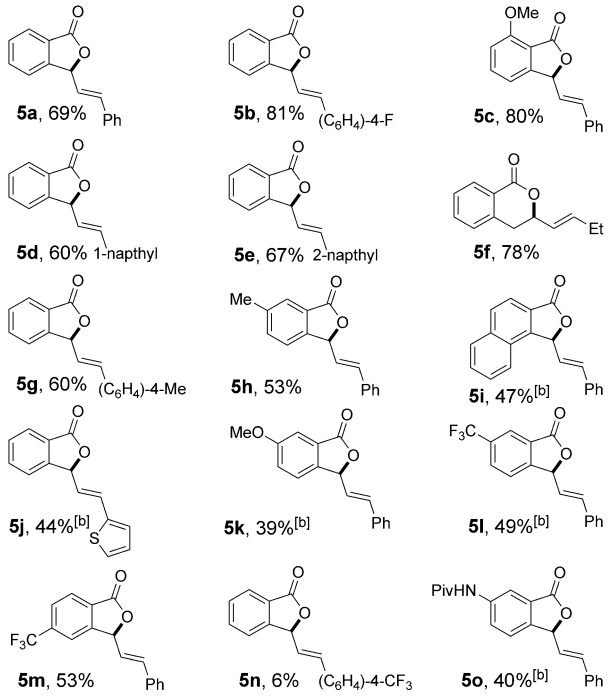
[a] Yield was determined by ^1H NMR spectroscopy using phthalide as an internal standard; [b] yield of isolated product. dppf = 1,1′-bis(diphenylphosphino)ferrocene; TFP = tri(2-furyl)phosphine; MS = molecular sieves; nc = no conversion.

on the overall yield. In addition to toluene, we also screened for others solvents, such as ethers (Table 1, entries 3–5), DMSO (entry 6), DMF (entry 7), nitromethane (entry 8), and hexane (entry 10). However, toluene gave the best results. Use of $(BnSe)_2$ as an alternative catalyst system resulted in a very low yield of only 5% (Table 1, entry 11). This result was attributed to the insufficient stability of this diselenide under the reaction conditions. To provide evidence that the allylic acyloxylation is solely selenium-catalyzed, we exposed substrate **4a** to 1 equivalent of NFSI in the absence of $(PhSe)_2$ (Table 1, entry 12). Under these conditions, product formation occurred only in trace amounts. We also wanted to exclude the possibility that minimal impurities of palladium, potentially arising from the substrate synthesis or the employed equipment, were actually responsible for the catalytic activity. Thus, we used both $[Pd(dppf)Cl_2]$ (Table 1, entry 13) and $[Pd(TFP)_2Cl_2]$ (entry 14; TFP = tri(2-furyl)phosphine), each in 5 mol%, as potential catalysts.[19] Neither of these experiments furnished the target structure **5a** in detectable amounts.

With optimized conditions in hand, we continued with the exploration of the scope and limitations of the title transformation (Table 2). In general, the selenium-catalyzed C(sp^3)–H acyloxylation is compatible with various *ortho*-allyl benzoic acid derivatives. Phthalides **5** were formed in reasonable to good yields (39–81%) and with high chemoselectivity in favor of the C(sp^3)–H oxidation. Both electron-withdrawing and electron-donating groups attached to the benzoic acid unit were well tolerated. More specifically, we tested substrates containing methoxy and methyl substituents in the 5- and 6-position of the benzoic acid entity (Table 2; products **5c**, **5h**, and **5k**). Such a substitution pattern is very prominent in a number of biologically active phthalide natural products, such as isoochra-

Table 2. Substrate scope of the selenium-catalyzed C(sp^3)–H acyloxylation.[a]

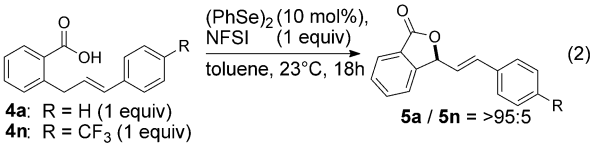




[a] Reaction conditions (unless indicated otherwise): **4a–o** (0.14–0.29 mmol), NFSI (1.0 equiv), catalyst (10 mol%), molecular sieves (4 Å), toluene (0.1–0.2 M), 18–24 h, 23 °C; yields correspond to isolated products. [b] Yield was determined by ^{1}H NMR spectroscopy using phthalide as an internal standard.

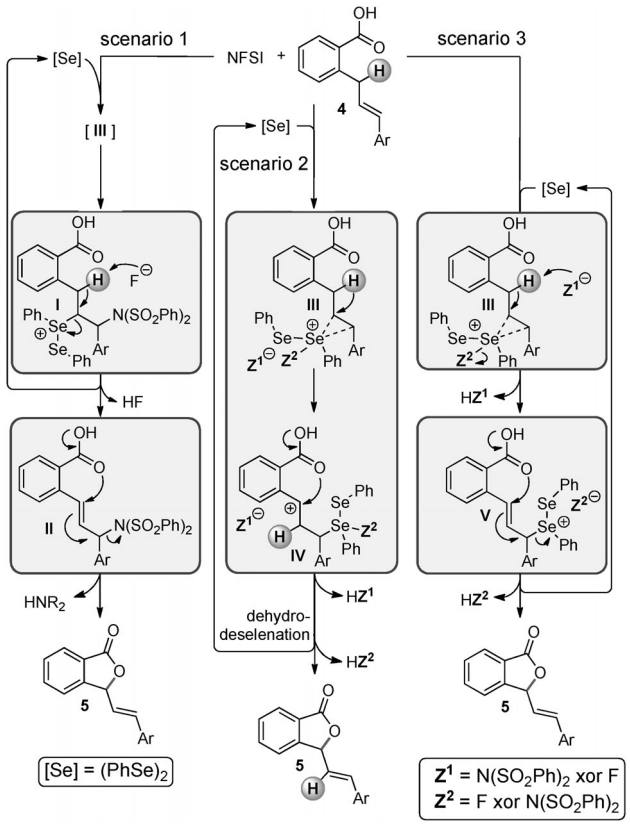
cinic acid, (+)-spirolaxine, and chrysoarticulin C (Scheme 1).[16] Substrates **4l** and **4m**, which contain electron-withdrawing CF_3 groups at the 4- and 5-position, respectively, furnished the phthalides **5l** and **5m** in yields of 49 and 53%, respectively. We also analyzed the influence of electronically varying substitution patterns at the olefin moiety. Whereas electron-neutral groups (Table 2, products **5a**, **5c–e**, and **5g**) and substituents exerting a positive mesomeric effect (Table 2, products **5b** and **5o**) generally resulted in moderate to good yields (44–81%), electron-deficient systems, such as CF_3-substituted substrate **4n**, suffered from severely lowered conversion, which is presumably due to the electron-withdrawing effects on the conjugated olefin unit (Table 2, Equations 2 and 5). In contrast, we found that a thiophene substituent resulted in a 44% yield in the allylic acyloxylation (Table 2, product **5j**). A remarkable switch in selectivity was observed during the formation of compound **5f**, since 6-*exo*-trig cyclization was preferred over C(sp^3)–H lactonization. At this point, a detailed understanding of the mechanistic parameters governing the change in product selectivity remains elusive. However, we speculate that the replacement of an aryl group for a sterically less-demanding and electronically less-stabilizing alkyl group results in a 1,2-oxyselenation of the double bond, upon which elimination of the selenium entity presumably leads to the formation of **5f**.[20]

In addition to the substrate scope, we were also interested in obtaining insights into the mechanism of the selenium-catalyzed C(sp^3)–H acyloxylation. Considering results previously obtained in the oxidative allylic amination of linear olefins,[13] we postulated that NFSI initially reacts with the diselane catalyst to form an electrophilic selenonium species, which may directly react with the C=C double bond. This hypothesis is supported by a competition experiment between **4a** (1 equiv) and **4n** (1 equiv) in the presence of NFSI (1 equiv) and $(PhSe)_2$ (10 mol%) under otherwise standard conditions [(Equation 2)].



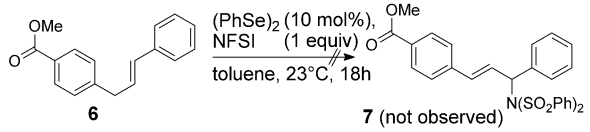
During the course of the reaction, the more electron-rich derivative **4a** reacted much faster, whereas the majority of compound **4n** remained intact. In combination with the fact that the C–H cleavage at the methylene moiety itself has no impact on the overall reaction rate (Equation 5), these findings suggest that the C–C double bond is collaterally involved in the C–O bond forming event at the adjacent sp^3-hybridized carbon center. To provide a rationale for our experimental results, we considered three possible scenarios (Scheme 2): Scenario 1) the reaction may proceed through a sequence consisting of an allylic imidation with concomitant transposition of the C=C double bond, leading to imide **II** through transient formation of intermediates **III** and **I**.[13] Subsequent S_N2' displacement of the imide group may then lead to product **5**. Scenario 2) The mechanism may alternatively involve a 1,2-hydride shift upon reaction of the Se electrophile with the C=C double bond (intermediate **III**),[21] which would lead to the formation of benzylic carbocation **IV**. Interception of cation **IV** by the proximal carboxylate group would eventually give rise to target structure **5** upon dehydrodeselenation. Scenario 3) In the last scenario, an allylic selenation with simultaneous relocation of the C–C double bond may take place to furnish intermediate **V**.[22] In analogy to scenario 1, the carboxylate function may undergo a S_N2' displacement of the selenium nucleofuge, which would finally lead to product **5**.

To determine whether the C(sp^3)–H acyloxylation proceeds through a sequential allylic amination/S_N2' displacement (scenario 1), we subjected methyl 4-cinnamylbenzoate (**6**) to the standard reaction conditions. We suspected compound **6** to be electronically equivalent to substrate **4a** but geometrically unsuited for intramolecular lactonization [Equation (3)]. Subjecting compound **6** to the standard reaction conditions did not furnish imidation product **7**, suggesting that scenario 1 is an implausible pathway. Next, we exposed deuterated analog

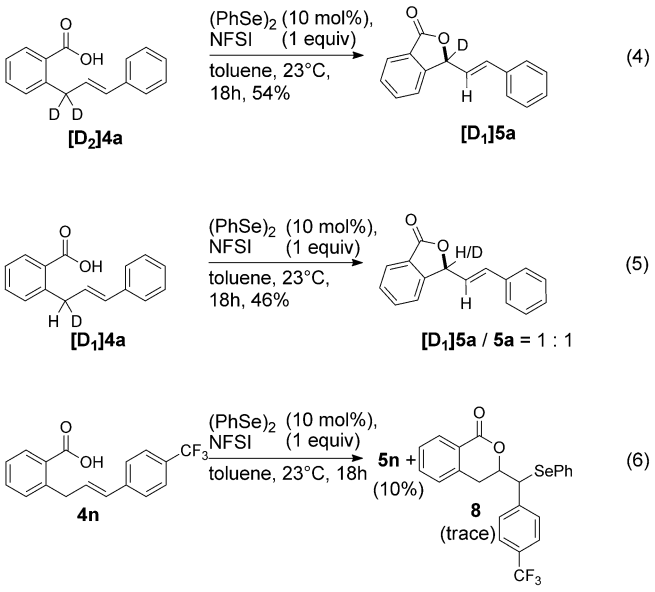


Scheme 2. Working hypotheses for the selenium-catalyzed C(sp^3)–H acyloxylation. The acronym "xor" denominates an exclusive disjunction between Z^1 and Z^2, thus, $Z^1 = N(SO_2Ph)_2$ only if $Z^2 = F$ or vice versa.

[D_2]**4a** to NFSI (1 equiv) and 10 mol% of $(PhSe)_2$ with the intention to provide an answer to the question as to whether a 1,2-hydride shift is operative during the oxidative lactonization step. However, no deuterium incorporation into the alkene entity of product **5** was detected, which disproved scenario 2 as a reasonable reaction mechanism [Equation (4). Furthermore, we could show that scission of the C–H bond of the methylene moiety was not rate limiting, since conversion of monodeuterated substrate [D_1]**4a** showed no kinetic isotope effect [Equation (5)]. As was discussed earlier, the electronic nature of the alkene unit adjacent to the sp^3-hybridized carbon atom has a significant impact on the reaction rate [Equation (2)]. From our previous studies,[13] we learned that $(PhSe)_2$ does not undergo significant oxidative fragmentation (e.g., through SET mechanisms)[23] caused by NFSI under operational reaction conditions. Therefore, we suspect that formation of the C–O bond via radical mechanisms is unlikely. Moreover, closer inspection of the oxidative cyclization of substrate **4n** to isobenzofuranone **5n** led to the discovery of byproduct **8** in trace amounts [Equation (6)].[24]



(3)



This finding is indicative of an initial attack of a transiently formed selenium electrophile onto the C=C double bond, presumably leading to cationic intermediate **III** (Scheme 2).[13,21] This, in turn, can undergo either direct nucleophilic attack by the carboxylate group, which, upon cleavage of the Se–Se bond, eventually results in the formation of compound **8**, or it can undergo deprotonation to transiently yield intermediate **V**.[22] This species may eventually undergo an S_N2' reaction leading to product **5** and the selenium catalyst. In consideration of all of the aforementioned factors, we conclude that the title transformation most likely proceeds according to scenario 3. It should be noted, however, that further investigations are necessary and currently ongoing to provide a clear and complete picture of the mechanism that is operative in the allylic C(sp^3)–H acyloxylation.

In summary, we have reported an unprecedented organodiselane-catalyzed intramolecular oxidative C(sp^3)–H acyloxylation of simple *ortho*-allyl benzoic acids, using NFSI as the terminal oxidant. The title procedure allows for a direct and chemoselective synthetic route towards the isobenzofuranone skeleton, a structural motif common to a large number of phthalide natural products. It should be pointed out that the allyl groups present in the lactone products **5** offer the opportunity for facile further derivatization, thus, rendering compounds **5** versatile building blocks in the context of synthetic applications.[25] Mechanistically, the reaction is hypothesized to proceed through an allylic selenation/S_N2'-substitution domino reaction. However, further mechanistic studies will be conducted in due course to corroborate our postulate. Nonetheless, we anticipate our protocol to expediently complement the current repertoire of cognate transition-metal-catalyzed C(sp^3)–H acyloxylations. Currently, investigations toward the development of an asymmetric variant of this reaction, as well as its implementation into the total synthesis of phthalide natural products, are ongoing.

Experimental Section

Representative procedure: Diphenyl diselenide (3.8 mg, 12 μmol, 0.10 equiv) was added to a solution of (*E*)-2-[3-(4-fluorophenyl)-2-propen-1-yl]benzoic acid (**4b**; 31.0 mg, 121 μmol, 1.00 equiv), *N*-fluorobenzenesulfonimide (38.2 mg, 121 μmol, 1.00 equiv) and molecular sieves (4 Å) in toluene (1.5 mL). The reaction mixture was stirred for 16 h at room temperature. Evaporation of the solvent and flash column chromatography (SiO_2, 10:1 petroleum ether/ethyl acetate) afforded compound **5b** (24.8 mg, 97.5 μmol, 81%) as a colorless oil.

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Keywords: alkenes · C–O coupling · oxidation · reaction mechanisms · selenium

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[16] For a recent review, see: R. Karmakar, P. Pahari, D. Mal, *Chem. Rev.* **2014**, *114*, 6213.

[17] ^{1}H NMR spectroscopic data are in accordance with those reported in the following references: Compound **2a**: H. Yang, G.-Y. Hu, J. Chen, Y. Wang, Z.-H. Wang, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5210; compound **3a**: F. M. Hauser, V. M. Baghdanov, *J. Org. Chem.* **1988**, *53*, 4676.

[18] The structures of both substrate **4a** and product **5a** were assigned on the basis of 2D ^{1}H NMR spectroscopic data. For literature reports on congruent ^{1}H NMR spectroscopic data of compound **5a**, see: Z. Ye, G. Lv, W. Wang, M. Zhang, J. Cheng, *Angew. Chem. Int. Ed.* **2010**, *49*, 3671; *Angew. Chem.* **2010**, *122*, 3753.

[19] Both palladium complexes have been used in the synthesis of starting materials **4**.

[20] This type of cyclization is congruent with reports by other research groups. For representative examples, see: a) T. Nakamura, M. Oshida, T. Nomura, A. Nakazaki, S. Kobayashi, *Org. Lett.* **2007**, *9*, 5533; b) M. R. Huckstep, R. J. K. Taylor, M. P. L. Caton, *Tetrahedron Lett.* **1986**, *27*, 5919.

[21] At this point it is not fully clear whether the fluoride anion or the sulfonimide anion remains associated with the carbon-bound selenium atom. It may also be plausible that these species coexist in equilibrium.

[22] For representative examples of allylic selenations related to the intermediate step in the postulated mechanistic scenario 3, see: a) L.-P. Liu, M. Shi, *J. Org. Chem.* **2004**, *69*, 2805; b) T. Kawasaki, N. Onoda, H. Watanabe, T. Kitahara, *Tetrahedron Lett.* **2001**, *42*, 8003.

[23] a) G. Pandey, B. B. V. S. Sekhar, *J. Chem. Soc. Chem. Commun.* **1993**, 780; b) G. Pandey, V. J. Rao, U. T. Bhalerao, *J. Chem. Soc. Chem. Commun.* **1989**, 416; c) M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli, *Tetrahedron Lett.* **1989**, *30*, 1417.

[24] Byproducts analogous to compound **8** have been detected in all but one cyclization reaction in varying quantities. The only exception to this trend was found to be compound **5f**, for which no corresponding acyloxyselenation adduct was detected upon completion of the reaction.

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C–O Coupling

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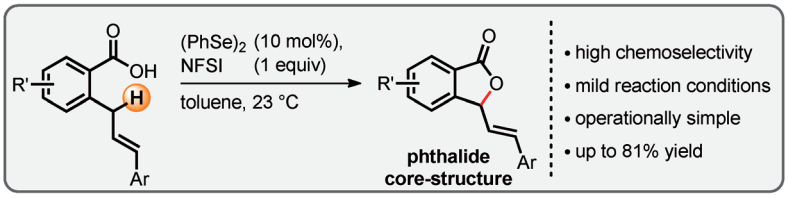
Selenium-Catalyzed C(sp^3)–H Acyloxylation: Application in the Expedient Synthesis of Isobenzofuranones



Allylic oxidation revisited: Oxidative intramolecular C(sp^3)–H acyloxylation of allylated benzoic acid derivatives through selenium catalysis is reported. This protocol provides direct access to the isobenzofuranone skeleton, a structural motif frequently found in phthalide natural products, in yields of up to 81% using *N*-fluorobenzenesulfonimide (NFSI) as the terminal oxidant.