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Catalytic and Atom-Economic Intermolecular Amidoselenenylation of Alkenes

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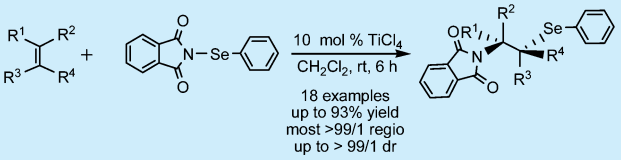
Supporting Information

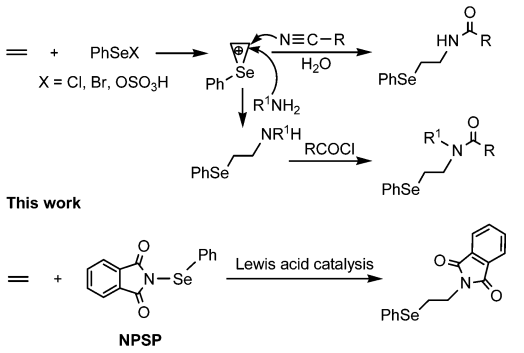
ABSTRACT: A method for the simple, efficient, and atom-economic amidoselenenylation of simple alkenes under mild conditions using $TiCl_4$ as a catalyst and *N*-(phenylseleno)-phthalimide as both a nitrogen and selenium source was developed. A broad range of olefins can be applied to afford vicinal amidoselenides in good yield and with high regioselectivity and diastereoselectivity.



As basic structural moieties, amides widely exist in bioactive natural products and pharmaceuticals.[1] Therefore, the efficient incorporation of an amido group into organic molecules has drawn much attention. Organoselenium compounds continue to be extensively studied because of their recognized biological activities.[2] The antioxidant properties and mimetic activity of some selenoenzymes such as thioredoxin reductases (TrxRs), selenophosphate synthetase, and selenoprotein P, in addition to the well-known glutathione peroxidase (GPx), which contains a selenocysteine residue at the active site, are well-established, making these compounds interesting synthetic targets.[3] Organoselenium compounds have been widely used as versatile reagents in organic synthesis, playing an important role in a wide range of transformations.[4] We speculated that if both the selenium atom and amido group can be simultaneously installed into the carbon−carbon double bond, a variety of vicinal amidoselenides could be easily accessed from simple alkenes, which we expect would provide efficient access to selenocysteine.

The selenofunctionalization of olefins using electrophilic organoselenium reagents represents an important method for the rapid introduction of vicinal functional groups, often with the concomitant formation of stereocenters.[5] Typically, the amidoselenenylation of olefins occurs via nucleophilic attack to a seleniranium intermediate with organonitrile as a nucleophile in the presence of water and trifluoromethanesulfonic acid (Scheme 1).[6] The reaction proceeds in poor yield on styrene and electron-rich olefins. In these cases, better yields were achieved by starting from the corresponding hydroxyselenylating or methoxyselenylating agent. Similar reactions have been conducted using different nitriles, affording the corresponding selenoamides.[7] Another approach to selenoamides is the acylation of the amino group in aminoselenides with a suitable acid chloride (Scheme 1).[8] Although *N*-(phenylseleno)-phthalimide (NPSP) is odorless and can provide a convenient source of electrophilic selenium, realizing the amidoselenenylation of olefins by using NPSP as a nitrogen and selenium source remains a substantial challenge because of the poor

Scheme 1. Synthesis of Vicinal Amidoselenides by an Intermolecular Addition Reaction of Alkenes and Organoselenide



nucleophilicity of the phthalimide counteranion, where good nucleophilicity is a prerequisite for a highly electrophilic seleniranium ion. Unfortunately, successful examples of such atom-economic processes are quite rare. Córsova reported the organocatalytic aminosulfenylation of α,β-unsaturated aldehydes; they obtained only one amidoselenenylation product by treating cinnamic aldehyde with *N*-(phenylseleno)succinimide, whereas they obtained both *syn*- and *trans*-diastereomers via the Michael addition mechanism.[9] However, the amidoselenenylation of styrene and electron-rich olefins has not been reported. On the basis of our research interests in the Lewis acid-catalyzed selenofunctionalization of olefins,[10] we herein disclose a Lewis acid-catalyzed intermolecular amidoselenenylation of alkenes with NPSP as both a nitrogen and selenium source under mild conditions and with high regioselectivity and diastereoselectivity.

Initially, (*E*)-β-methylstyrene (**1a**) was chosen as a model substrate with *N*-(phenylseleno)phthalimide[11] as both the

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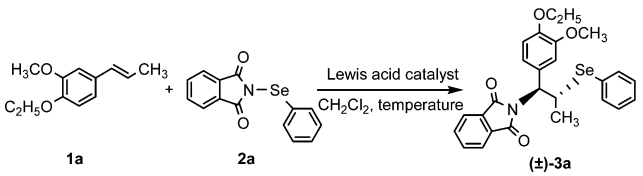
nitrogen/selenium source; this reaction was rather sluggish in the absence of catalyst, even under reflux conditions (Table 1, entries 1 and 2). An investigation using a series of Lewis acids and Brønsted acids identified TMSOTf and $TiCl_4$ as active catalysts. In the presence of 10 mol % of TMSOTf, the reaction proceeded smoothly at −78 °C for 2 h and then −20 °C for 4 h to afford the desired product in 75% yield (Table 1, entry 11). With an increase of temperature, the yield of product **3a** decreased, whereas β-hydroxyalkyl phenyl selenide, the product of the hydroxyselenenylation of an alkene, gradually became the main product. $TiCl_4$ (10 mol %) is a better catalyst, and the reaction was completed at room temperature in 6 h to afford a 93% yield of the desired product **3a**; no β-hydroxyalkyl phenyl selenide was observed in the product (Table 1, entry 16). In this case, the catalyst loading was reduced to 5 mol % to afford product **3a** in 80% yield (Table 1, entry 19). The yield of product **3a** did not increase with the increase of the amount of the catalyst (Table 1, entry 20 and 21).

Table 1. Optimization of the Intermolecular Amidoselenenylation of (*E*)-β-Methylstyrene (1a) and *N*-(Phenylseleno)phthalimide[a]

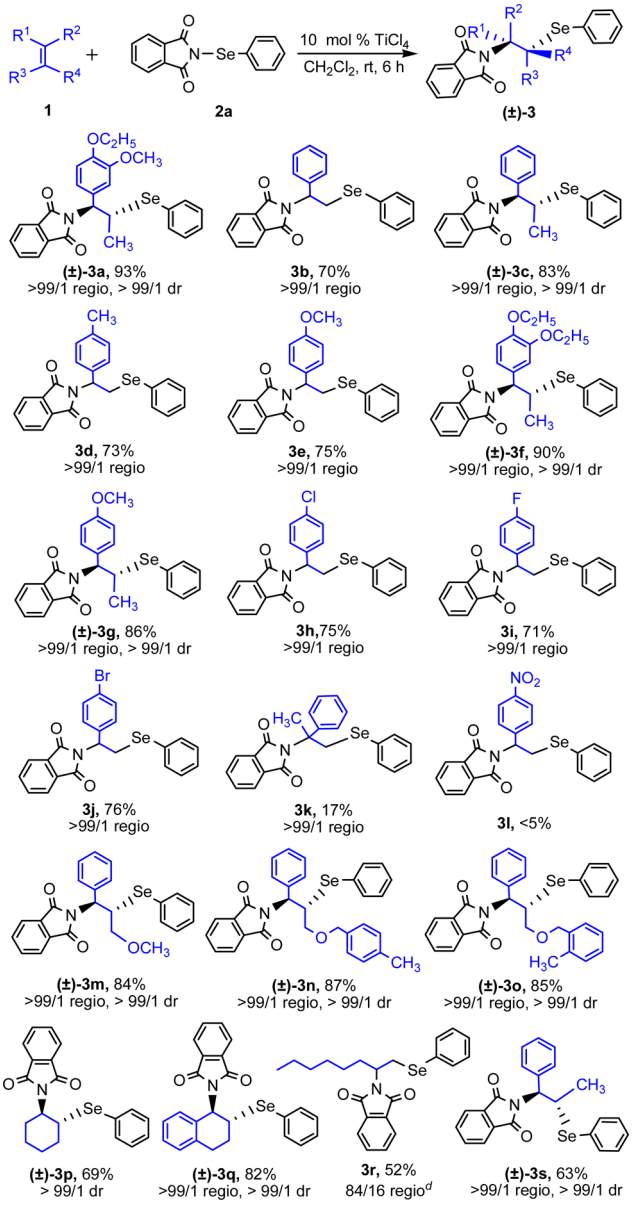


entry	catalyst	amt of catalyst (mol %)	temp (°C)	yield[b] (%)
1	none		rt	0
2	none		−78	0
3	TsOH	10	rt	0
4	$PhSO_3H$	10	rt	0
5	TFA	10	rt	0
6	$AlCl_3$	10	rt	0
7	$AgBF_4$	10	rt	0
8	$FeCl_3$	10	rt	0
9	$ZnCl_2$	10	rt	0
10	$SnCl_4$	10	rt	13
11	TMSOTf	10	−78 to −20	75
12	TMSOTf	10	−40	58
13	TMSOTf	10	−20	37
14	TMSOTf	10	0	20
15	TMSOTf	10	rt	15
16	$TiCl_4$	10	rt	93
17	$TiCl_4$	10	0	24
18	$TiCl_4$	10	−78	0
19	$TiCl_4$	5	rt	80
20	$TiCl_4$	20	rt	92
21	$TiCl_4$	40	rt	88

[a]The general reaction was carried out on a 0.5 mmol scale in 5 mL of CH_2Cl_2 for 6 h; the molar ratio of **1a**/**2a** was 1/1.10. [b]Isolated yield.

With the optimized conditions in hand, we next expanded the substrate scope; the results are shown in Scheme 2. In general, the reactions all proceeded smoothly to give products in good yields and with high regioselectivity. Styrene and styrene-bearing electron-withdrawing chloro, fluoro, and bromo substituents and electron-donating methyl, *p*-methoxyl, 3,5-diethoxyl, and 3-methoxyl-5-ethoxyl substituents gave good yields with 99% regioselectivity (Scheme 2, **3b**,**d**,**e**,**h**−**j**); by contrast, the strongly electron-withdrawing *p*-nitro substituent gave less than 5% yield (Scheme 2, **3l**). (*E*)-β-Methyl-, (*Z*)-β-methyl-, (*E*)-β-methoxymethyl-, and (*E*)-β-benzyloxymethylstyrenes gave good yields with 99% regioselectivity and diastereoselectivity (Scheme 2, **3a**,**c**,**f**,**g**,**m**−**o**,**s**), whereas α-methylstyrene gave 17% yield with 99% regioselectivity (Scheme 2, **3k**). These results indicate that the attack of the nucleophilic nitrogen at the episelenonium ion was governed by the steric effect of the substituent in the α-position of styrene, whereas substituents in the β-position promoted the amidoselenenylation of alkenes. In addition, both *E*- and *Z*-alkenes gave good results (Scheme 2, **3c**,**s**). Furthermore, Markovnikov-type adducts were obtained with good yields by

Scheme 2. Scope of the Intermolecular Amidoselenenylation of Alkenes and *N*-Phenylselenophthalimide[a]−[c]



[a]The general reaction was carried out on a 0.5 mmol scale in 5 mL of CH_2Cl_2; the molar ratio of **1**/**2a** was 1/1.10. [b]Isolated yield. [c]The value of dr was determined by ^1H NMR. [d]The reaction gave 52% yield of 2-(1-phenylseleno-2-octyl)-1*H*-isoindole-1,3(2*H*)-dione (**3r**) and 10% yield of 2-(2-phenylseleno-1-octyl)-1*H*-isoindole-1,3(2*H*)-dione (**3r′**).

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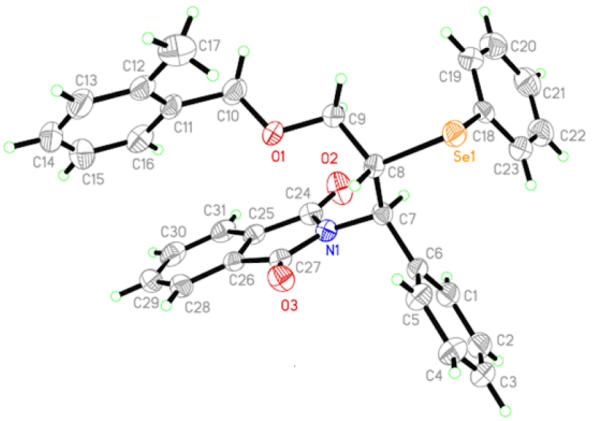
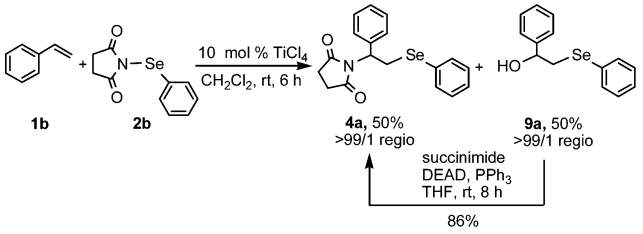
the highly regioselective amidoselenenylation of styrenes, and *trans*-type adducts were obtained regioselectively and diastereoselectively by amidoselenenylation of *β*-methylstyrenes and 1,2-dihydronaphthalene (Scheme 2, **3a,c,f,g,m−o,q,s**). The reaction also occurred smoothly with simple cyclic alkenes such as cyclohexene to give products with high diastereoselectivity (Scheme 2, **3p**). The relative stereochemistry of the reaction was indicated by the structural analysis of the crystal structure of **3o** (Figure 1). Long-chain alkenes such as 1-octylene, however, afforded adducts **3r** and **3r′** with low regioselectivity (Scheme 2, **3r**). According to the HMBC spectra of **3r**, the correlations of δ_C (168.6) and δ_H (7.75, 7.68, 4.41), and the correlation of δ_C (129.1) and δ_H (7.10, 3.68, 3.17), together with the ^{1}H NMR, ^{13}C NMR, and HSQC spectra, the following structure of compound **3r** can be deduced (Figure 2).



(±)-3o

Figure 1. ORTEP of the molecular structure of compound (±)-**3o**.

Scheme 3. Intermolecular Amidoselenenylation of Alkenes and *N*-Phenylselenosuccinimide[a,b]



[a]The general reaction was carried out on a 0.2 mmol scale in 5 mL of CH_2Cl_2; the molar ratio of **1b**/**2b** was 1/1.10. [b]Isolated yield.

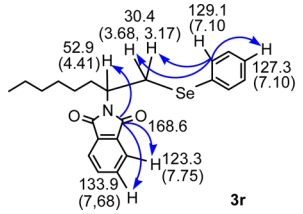
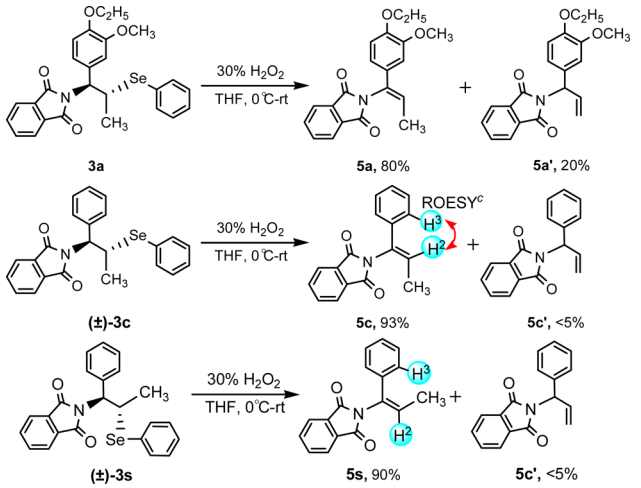


Figure 2. Long-range coupling correlations of carbon atoms (δ_C 168.6, 129.1) and the related hydrogen atoms in compound **3r**.

The reaction was next investigated in terms of another *N*-(phenylseleno)imide reagent, *N*-(phenylseleno)succinimide (NPSS) **2b**, resulting in 50% yield of amidoselenenylation product **4a** and 50% yield of hydroxyselenenylation product **9a**, both with 99% regioselectivity (Scheme 3). Treatment of other alkenes with NPSS mainly afforded hydroxyselenenylation products because the amidoselenenylation reactions were quenched with aqueous $NaHCO_3$ solution. However, the hydroxyselenylation product **9a** was treated with diethyl azodicarboxylate (DEAD) and triphenyl phosphine in THF at room temperature for 8 h to afford the desired product **4a** in 86% yield.

The regioselectivity of the products of the amidoselenenylation of alkenes was verified by the treatment of compounds **3a**, **3c**, and **3s** with 30% H_2O_2 aqueous solution in THF at 0 °C for 1.5 h and then at room temperature for 30 min to 3 h to afford **5a**, **5a′**, **5c**, and **5s** via a selenoxide *syn*-elimination reaction (Scheme 4). According to the ROESY spectrum of **5c**, the correlation of δ_H (7.32) and δ_H (6.51), together with the ^{1}H NMR, and ^{13}C NMR spectra, the structure of **5c** was verified to be (*Z*)-2-[1-phenyl-1-propenyl]-1*H*-isoindole-1,3(2*H*)-dione, whereas the structure of **5s** was verified to be (*E*)-2-[1-phenyl-1-propenyl]-1*H*-isoindole-1,3(2*H*)-dione. Therefore, the reaction of (*E*)-*β*-methylstyphene (**1a**) produces (1*S*,2*S*) and (1*R*,2*R*) adducts (±)-**3c**, and the reaction of (*Z*)-*β*-methylstyphene (**1s**) produces (1*S*,2*R*) and (1*R*,2*S*) adducts (±)-**3s** (Scheme 4).

Scheme 4. Selenoxide *syn*-Elimination of Compound 3a, 3c, and 3s[a,b]



[a]The general reaction was carried out on a 0.2 mmol scale in 8 mL of THF, in the presence of H_2O_2 aqueous solution (0.5 mL). [b]Isolated yield. [c]The correlation of δH^3 (7.32) and δH^2 (6.51) in the ROESY spectrum of **5c**.

Mechanistically, the amidoselenenylation reaction is proposed to occur via the typical episelenonium ion intermediate **8** (Scheme 5). In this scenario, $TiCl_4$ may promote the formation of a three-membered-ring seleniranium ion with high electrophilicity by chelation to the amide carbonyl group (**6**); most importantly, the in situ generated phthalimide anion (**7**) would have sufficient solubility and nucleophilicity to participate in nucleophilic attack in situ because of its benzo-conjugate nature. The observation of *trans*-type adducts supports the proposed mechanism. In addition, the amidoselenenylation

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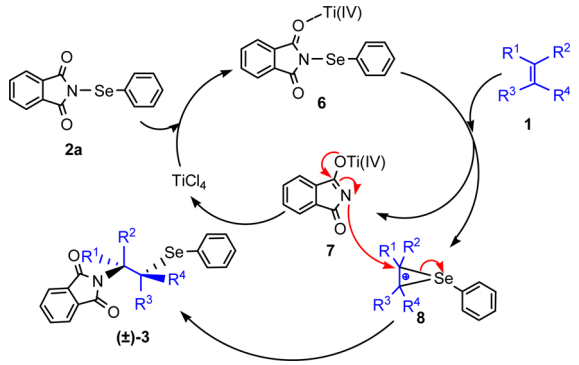
Scheme 5. Proposed Mechanism for the Intermolecular Amidoselenenylation of Alkenes and *N*-(Phenylseleno)phthalimide[a,b]



reaction at room temperature affords the thermodynamically more stable Markovnikov adducts.

In conclusion, we have developed a catalytic, simple, efficient, atom-economic, and regioselective and diastereoselective amidoselenenylation reaction of electron-rich alkenes using *N*-(phenylseleno)phthalimide as both a nitrogen and selenium source. The use of phthalimide-type electrophilic selenium reagents is also synthetically appealing because such an *N*-protection moiety can be readily removed for subsequent transformations. Investigations of the enantioselective amidoselenenylation reaction are currently ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03157.

Experimental procedures and ^{1}H NMR and ^{13}C NMR spectral data for compounds **3**, **4a**, **5a**, **5a′**, **5c**, **5s**, and **9a**, HSQC and HMBC spectral data for compound **3r**, crystal data of compound **3o**, and ROESY spectra for compounds **5c** and **5s** (PDF)

X-ray data for **3o** (CIF)

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Notes

The authors declare no competing financial interest.

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