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Efficient Synthesis of Chiral β-Seleno Amides via Ring-Opening Reaction of 2-Oxazolines and Their Application in the Palladium-Catalyzed Asymmetric Allylic Alkylation

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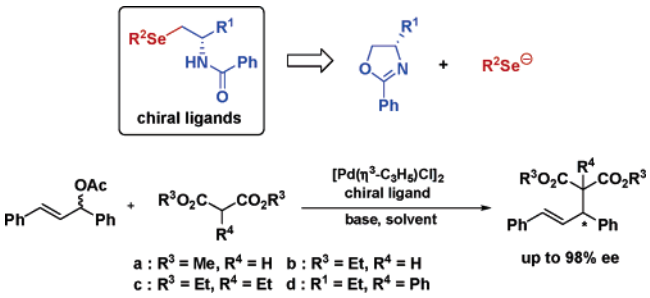

A set of chiral β-seleno amides have been efficiently synthesized via the ring-opening reaction of chiral 2-oxazolines by selenium nucleophiles. The present method is applicable to the synthesis of β-seleno amides containing thioether, alcohol, and ether moieties in good yields. As an application, the synthesis of a selenocysteine derivative has been accomplished. Additionally, these new compounds were evaluated in the palladium-catalyzed asymmetric allylic alkylation, giving the alkylated products in up to 98% ee.

Organoselenium chemistry has emerged as an exceptional class of structures in recent years, due to its pivotal role in the synthesis of a large number of biological compounds (e.g., selenocarbohydrates, selenoamino acids, and selenopeptides) and as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[1] Indeed, recent advances in the synthesis of compounds containing selenium have been driven by their interesting reactivities[2] and their potential pharmaceutical significance.[3] In particular, chiral selenium-based methods have received special attention of organic chemists in the past decade and are now a very important tool for stereoselective transformations.[4]

On the other hand, enantiopure 2-oxazolines, biologically relevant heterocycles widely found in nature,[5] represent a versatile and useful class of compounds in organic transformations.[6] Among the many applications to organic synthesis, these compounds can undergo ring-opening reactions with nucleophiles, resulting in interesting β-substituted compounds containing heteroatoms such as N and O.[7]

At the same time, some of the more exciting areas of research using chiral organoselenium compounds have been catalytic asymmetric reactions to provide enantiomerically enriched compounds, representing a new trend in this field of organometallic chemistry. In this context, chiral selenide- and diselenide-containg ligands have been employed as useful catalysts in various asymmetric transformations such as enantioselective addition of diethylzinc to aldehydes,[8,9] 1,4-addition of Grignard reagents to enones,[10] and palladium-catalyzed asymmetric allylic substitution.[11,12] The last transformation is currently among the most important transition-metal-catalyzed reactions known to form carbon−carbon and carbon-heteroatom bonds,[13] and it is a widely applied process in the synthesis of optically active small molecules and in the total synthesis of natural products.[14]

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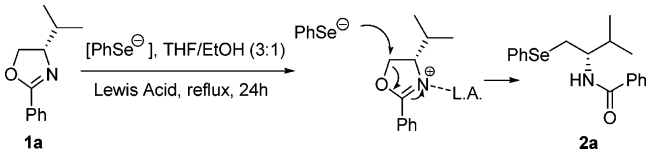
TABLE 1. Ring-Opening Reactions of Oxazoline 1a on Varying the Phenyl Selenide Anion and the Lewis Acid



entry	[PhSe⁻]	Lewis acid (amt (equiv))	yield (%)[a]
1	$(PhSe)_2/NaBH_4$		40
2	$(PhSe)_2/NaBH_4$	$TiCl_4$ (2)	no reacn
3	$(PhSe)_2/NaBH_4$	Bu_3SnCl (2)	21
4	$(PhSe)_2/NaBH_4$	$BF_3.OEt_2$ (2)	63
5	$(PhSe)_2/NaBH_4$	TMSCl (2)	80
6	$(PhSe)_2$/*n*-BuLi	TMSCl (2)	51
7	$(PhSe)_2$/Na	TMSCl (2)	12
8	$(PhSe)_2/NaBH_4$	TMSCl (4)	82
9	$(PhSe)_2/NaBH_4$	TMSCl (1)	79
10	$(PhSe)_2/NaBH_4$	TMSCl (1)	93[b]
11	$(PhSe)_2/NaBH_4$	TMSCl (0.5)	52

[a] Isolated yield of the corresponding product. [b] TMSCl was freshly distilled.

In the course of our growing interest in the preparation of chiral organoselenium compounds and their application in asymmetric synthesis,[9,10,12] we describe herein the behavior of 2-oxazolines in the presence of various selenium nucleophiles in order to get an easy, inexpensive, and straightforward access to chiral β-seleno amides and their derivatives by a ring-opening process. Furthermore, these new compounds were evaluated as chiral ligands in the palladium-catalyzed asymmetric allylic alkylation.

As outlined in the sequence shown in Table 1, the preparation of the β-seleno amides proceeds through the formation of an oxazolinium intermediate, and the regio- and chemoselective nucleophilic attack of the phenyl selenide anion at the C(5) position of the ring leads to C(5)−O(1) bond cleavage and furnishes the desired product **2a**, without any loss of enantiomeric purity, as determined by chiral HPLC. Compounds similar to **2a** were synthesized by Tiecco et al. via asymmetric azidoselenenylation of alkenes and efficiently applied as synthetic intermediates in the synthesis of important enantiomerically enriched nitrogen-containing heterocycles.[15]

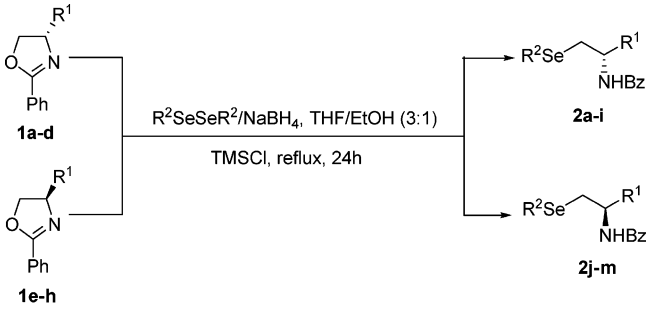
The reaction was initially studied with the compound **1a** and phenyl selenide anion, easily generated by reduction of PhSeSePh with $NaBH_4$ in a mixture of THF and EtOH, in the absence of Lewis acid. However, under these conditions the product was obtained in only 40% yield (Table 1, entry 1). Therefore, this result prompted us to better investigate the present reaction, varying the Lewis acid (2 equiv), since this additive could increase the electrophilic character of the heterocycle. Surprisingly, when the reaction was carried out with $TiCl_4$ and Bu_3SnCl, quite disappointing results were obtained (Table 1, entries 2 and 3). Probably, in both cases, the complex formed between the oxazoline and the Lewis acid was not as efficient in affording the new C−Se bond. The treatment of oxazoline **1a** with $BF_3{\cdot}OEt_2$ and TMSCl was studied as well (Table 1, entries 4 and 5). With $BF_3{\cdot}OEt_2$, the product was obtained in 63% yield, while using TMSCl under the same conditions, the most efficient ring-opening process was achieved. We also varied the counterion of the selenium nucleophile. Thus, the phenyl selenide anion was generated by reduction of PhSeSePh with *n*-BuLi or metallic Na, respectively. However, for both, no improvement could be observed (Table 1, entries 6 and 7).

With these results, the amount of TMSCl was also evaluated. It could be observed that the yield has only slightly increased on increasing the amount of TMSCl (Table 1, entry 8). However, the best results were obtained when 1.0 equiv of freshly distilled TMSCl was employed in the reaction, resulting in a highly effective degree of complexation of the Lewis acid and the nitrogen atom present in the oxazoline moiety (Table 1, entry 10).

After we chose the best manner to generate the selenium nucleophile and the most appropriate amount of the Lewis acid, the present reaction was further expanded to a broader range of oxazolines in order to evaluate the scope and limitations of the reaction procedure.

As delineated in Table 2, we could observe that all the β-seleno amides were obtained in good to excellent yields for the oxazolines studied (Table 2, entries 1−8), except

TABLE 2. Ring-Opening Reaction of Oxazolines 1a−h



entry	oxazoline	R^1	R^2	compd, yield (%)[a,b]
1	**1a**	*i*-Pr	Ph	**2a**, 93
2	**1b**	*i*-Bu	Ph	**2b**, 82
3	**1c**	Bn	Ph	**2c**, 84
4	**1a**	*i*-Pr	Bu	**2d**, 27
5	**1a**	*i*-Pr	Bn	**2e**, 71
6	**1a**	*i*-Pr	2,4,6-Me_3Ph	**2f**, 79
7	**1a**	*i*-Pr	*p*-ClPh	**2g**, 82
8	**1a**	*i*-Pr	*p*-MeOPh	**2h**, 84
9	**1d**	$(CH_2)_2SMe$	Ph	**2i**, 72
10	**1e**	CH_2OH	Ph	**2j**, 90
11	**1f**	CH_2OBn	Ph	**2k**, 78
12	**1g**	CH_2OEt	Ph	**2l**, 87
13	**1h**	COOMe	Ph	**2m**, 51

[a] Isolated yield of the corresponding product. [b] TMSCl was freshly distilled.

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when dibutyl diselenide was used as the nucleophilic source of selenium (Table 2, entry 4). The nature of the side chain at the oxazoline does not play a significant role in terms of conversion to the desired product, since the results obtained with different lipophilic groups were quite similar.

It could be also noted that the aromatic diselenide containing an electron-withdrawing group such as chloro and an electron-donating group such as methoxy does not exert a strong electronic influence, as the products were obtained in 82% and 84% yields, respectively (Table 2, entries 7 and 8). As a further extension of the present approach, we attempted to synthesize several chiral β-seleno amide compounds bearing interesting functionalities such as thioether (Table 2, entry 9), alcohol (Table 2, entry 10), and ether (Table 2, entries 11 and 12), constituting an efficient way to prepare β-seleno amides and their derivatives in a short and convenient sequence.

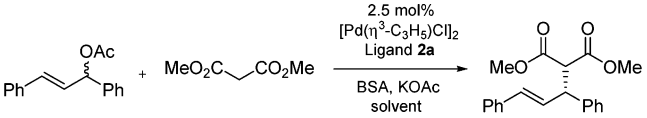
Due to their potential biological activity in the past few years, some recent and classical successful approaches have been documented, aimed at the synthesis of selenocysteine and its derivatives.[16] In this context, a formidable challenge still remains to develop novel synthetic methods that can permit the introduction of selenium into optically active amino acids, which could be widely explored as building blocks for the synthesis of seleno peptides and derivatives.[16c,d] Thus, we also focused our attention on the synthetic usefulness of this method by an application in the synthesis of a selenocysteine derivative, employing the 2-oxazoline-4-carboxylate **1h** as starting material (Table 2, entry 13).

Although the desired analogue **2m** has been synthesized in modest yield (51%), this route may constitute an attractive option for the preparation of various structurally diverse selenocysteine derivatives in the future, as the strategy presented herein involves only two steps and does not require the use of protecting groups such as Boc, Cbz, and Fmoc.

Taking into consideration that mixed Se,N compounds represent an interesting and efficient class of ligands in chirality transfer concerning the metal-catalyzed asymmetric reactions and that only few examples of chiral ligands containing a selenium atom coordinated to palladium have been described in the literature,[11,12] we decided to investigate the catalytic performance of compounds **2** in palladium-catalyzed asymmetric allylic alkylation.

Initially, we studied the palladium-catalyzed asymmetric allylic alkylation (AAA) of 1,3-diphenyl-2-propenyl acetate (**3**) with dimethyl malonate (**4a**) in the presence of 2.5 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and dichloromethane as solvent. The reaction was carried out with the β-seleno amide **2a** (10 mol %) in a mixture of *N,O*-bis(trimethylsilylacetamide) (BSA) and a catalytic amount of potassium acetate. To our surprise, the respective alkylated product (*R*)-**5a** was obtained in excellent yield and in 98% ee (Table 3, entry 1). This excellent result encouraged us to better evaluate the present asymmetric reaction. Thus, we examined the effect of the loading of the ligand **2a** (5 mol %), and under the same conditions the alkylated product was obtained at a similar level of chemical yield and excellent enantioselectivity (Table 3, entry 2). However, when the amount of the catalyst was decreased to 2.5 mol %, in the presence of 2.5 and 1.25 mol % of the palladium catalyst, the alkylated product was obtained in 93% and 82% ee, respectively (Table 3, entries 3 and 4). Thus, the best results were obtained by using 5 mol % of **2a** and 2.5 mol % of the palladium source, corresponding to a 1:1 ratio of ligand to palladium. The reaction was also carried out in the presence of LiOAc instead of KOAc and at lower temperature (0 °C), and no improvement could be achieved (Table 3, entries 5 and 6). We also examined the effect of the solvent on the reaction. When the solvent was changed from CH_2Cl_2 to other solvents, such as acetonitrile, THF, ether, and toluene, the product (*R*)-**5a** was obtained in good yields, however, with lower enantioselectivities (compare entries 2 and 7−11), showing that the solvent plays an important role in the enantioselection event.

TABLE 3. Palladium-Catalyzed Asymmetric Allylic Alkylation with β-Seleno Amide 2a[a]



3 **4a** (*R*)-**5a**

entry	amt of **2a** (mol %)	solvent	yield (%)[b]	ee (%)[c]
1	10	CH_2Cl_2	98	98
2	5	CH_2Cl_2	97	98
3	2.5	CH_2Cl_2	91	93
4[d]	2.5	CH_2Cl_2	84	82
5[e]	5	CH_2Cl_2	94	96
6[f]	5	CH_2Cl_2	81	98
7	5	CH_3CN	89	79
8	5	THF	83	61
9	5	ether	87	78
11	5	toluene	82	59
12[g]	5	CH_2Cl_2	89	63

[a] All reactions were carried out for 24 h at room temperature. [b] Isolated yields. [c] Conditions: determined by HPLC with a Chiralcel OD column; hexane/2-propanol 99:1; 0.5 mL/min; 254 nm. [d] 1.25 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was used instead of 2.5 mol %. [e] LiOAC was used instead of KOAc. [f] Reaction was carried out for 48 h at 0 °C. [g] *rac*-1,3-Diphenyl-2-propenyl ethyl carbonate was used instead of **3**.

After choosing the best system to promote the palladium-catalyzed allylic alkylation and prompted by the results obtained with ligand **2a**, we extend our studies to the present reaction, and the results are summarized in Table 4.

We could observe that the nature of the group R^2 attached to the selenium atom does not play a significant role in terms of yield and enantioselectivities, once all the β-seleno amides **2a**−**h** furnished the alkylated product in good to excellent results. Ligands with alkyl groups such as **2d** (R^2 = Bu) and **2e** (R^2 = Bn) at the selenium donor showed high efficiency in the asymmetric reaction and afforded the corresponding products in 97% and 96% ee, respectively (Table 4, entries 4 and 5). Steric and

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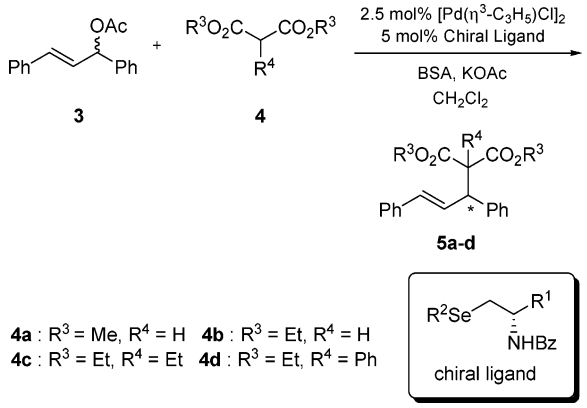
TABLE 4. Palladium-Catalyzed Asymmetric Allylic Alkylation with 2a−h



entry	ligand	R^1	R^2	malonate	yield (%)[a]	ee (%)[b,c]
1	**2a**	*i*-Pr	Ph	**4a**	97	98
2	**2b**	*i*-Bu	Ph	**4a**	95	89
3	**2c**	Bn	Ph	**4a**	90	88
4	**2d**	*i*-Pr	Bu	**4a**	96	97
5	**2e**	*i*-Pr	Bn	**4a**	94	96
6	**2f**	*i*-Pr	2,4,6-Me_3Ph	**4a**	89	91
7	**2g**	*i*-Pr	*p*-ClPh	**4a**	96	95
8	**2h**	*i*-Pr	*p*-MeOPh	**4a**	96	96
9	**2a**	*i*-Pr	Ph	**4b**	95	93
10	**2a**	*i*-Pr	Ph	**4c**	83	69
11	**2a**	*i*-Pr	Ph	**4d**	89	82

[a] Isolated yields. [b] Determined by chiral HPLC analysis. [c] For entries 1−9, the product has an *R* configuration. For entries 10 and 11, the absolute configuration of the product was not determined.

electronic effects with different substituents at the ring in the R^2 groups were also evaluated. A ligand with a bulkier group, **2f** (R^2 = 2,4,6-Me_3Ph), and ligands containing an electron-withdrawing group, **2g** (R^2 = *p*-ClPh), and an electron-donating group, **2h** (R^2 = *p*-MeO), furnished (*R*)-**5a** in good yields and excellent enantioselectivities ranging from 91 to 96% (Table 4, entries 6−8), showing that steric and electronic effects do not reduce the ability of the selenium to coordinate to the palladium atom.

In addition, we examined the AAA reaction of various dialkyl malonates using **2a** as a ligand. The alkylated products **5b−d** were obtained with different levels of enantioselectivity and in good to excellent yields (Table 4, entries 9−11). Although the desired products have been achieved in moderate to good enantioselectivities, to the best of our knowledge, selenium-containing ligands have not been evaluated with several dialkyl malonates in the present reaction.

The ligands **2i−m** were also studied in the usual catalytic system. The presence of other functional groups in the β-seleno amides such as thioether, alcohol, ether, and ester has a negative effect on the reaction, giving the respective essentially racemic alkylated products with a very low yield.

In summary, we have shown a practical and concise synthesis of a wide range of chiral β-seleno amides and their derivatives by an easy, straightforward, and flexible synthetic route, starting from chiral 2-oxazolines. In addition, further improvements to extend the present methodology to the synthesis of selenocysteine analogues are underway in our laboratory.

These new compounds were systematically performed in the palladium-catalyzed asymmetric allylic alkylation, and the respective alkylated products were obtained in excellent enantiomeric excess. We also believe that this modular approach may have significant importance in the design of new chalcogen-containing compounds for asymmetric catalysis as well as the synthesis of interesting compounds for biological screenings.

Experimental Section

General Procedure for the Synthesis of Chiral β-Seleno Amides 2. Under an argon atmosphere, freshly distilled TMSCl (1 mmol) was added to a solution of the appropriate oxazoline **1** (1 mmol) in dry THF (4 mL). The mixture was stirred for at least 30 min. The selenide anion was generated by reaction of the corresponding diselenide (0.6 mmol) with $NaBH_4$ (1.5 mmol) in a mixture of THF (1.5 mL) and EtOH (0.5 mL) and transferred to the flask containing the oxazolium intermediate. The resulting solution was stirred for 24 h under reflux. The mixture was quenched with a saturated NH_4Cl solution and extracted with CH_2Cl_2, and the combined organic fractions were collected, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, yielding the crude products **2a−m**, which were purified by flash chromatography.

(*S*)-*N*-(3-Methyl-1-(phenylselanyl)butan-2-yl)benzamide (2a). The enantiomeric purity was determined by HPLC analysis (column Chiralcel-OD, eluent hexane/2-propanol 90:10, flow rate 1.0 mL min^{-1}; *R* isomer (t_R = 9.33 min), *S* isomer (t_R = 13.47 min)) and found to be >99.9%: yield 0.322 g (93%); white solid; mp 101−103 °C; $[\alpha]_D^{20}$ = +210° (*c* = 1.0, CH_2Cl_2); IR (KBr) 3313, 2965, 1633, 1533, 1470, 1178, 733, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.35 (m, 7H); 7.25−7.19 (m, 3H); 6.29 (d, *J* = 8.4, 1H); 4.22 (m, 1H); 3.25−3.23 (m, 2H); 2.05−2.00 (m, 1H); 0.98−0.96 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 134.5, 132.7, 131.1, 129.9, 129.1, 128.3, 126.9, 126.7, 54.7, 31.7, 31.6, 19.3, 18.5; ^{77}Se NMR ($CDCl_3$) δ 251.5; HRMS-ESI *m/z* calcd for $C_{18}H_{21}NOSe + Na^+$ 370.0680, found 370.0677.

(*R*)-Methyl 2-Benzamido-3-(phenylselanyl)propanoate (2m). Data for **2m** are as follows: yield 0.185 g (51%); white solid; mp 74−76 °C; $[\alpha]_D^{20}$ = +35° (*c* = 1.0, CH_2Cl_2); IR (KBr) 3359, 3073, 2960, 1741, 1649, 1516, 1208, 1162, 742, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61−7.19 (m, 10H), 6.95 (d, *J* = 7.2, 1H), 5.19−5.14 (m, 1H), 3.55−3.51 (m, 4H), 3.42 (dd, *J* = 13.6, *J* = 4.8, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 166.7, 133.3, 133.2, 131.2, 129.1, 128.5, 128.3, 127.4, 126.9, 52.6, 52.3, 29.8; ^{77}Se NMR ($CDCl_3$) δ 268.5; HRMS-ESI *m/z* calcd for $C_{17}H_{17}NO_3Se + Na^+$ 386.0265, found 386.0261.

General Procedure for the Palladium-Catalyzed Asymmetric Allylic Alkylation. Under an argon atmosphere, a solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) and chiral ligand (5 mol %) in CH_2Cl_2 (2 mL) was stirred for 30 min at room temperature. Subsequently, a solution of *rac*-1,3-diphenyl-2-propenyl acetate (0.5 mmol), dialkyl malonate (1.5 mmol), *N,O*-bis(trimethylsilylacetamide) (BSA; 1.5 mmol), and KOAc (catalytic quantity) were added. The resulting solution was stirred for 24 h. The mixture was quenched with a saturated NH_4Cl solution and extracted with CH_2Cl_2, and the combined organic fractions were collected, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, yielding the respective alkylated products **5a−d**, which were purified by flash chromatography.

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Supporting Information Available: Text and figures giving full experimental procedures and characterization data for the compounds discussed in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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